A.M.A. Archives OF

NEUROLOGY AND PSYCHIATRY

INDEX NUMBER

NEUROLOGY SECTION

Studies on Headache
Ernst Pichler, Adrian M. Ostfeld, Helen Goodell, and Harold G. Wolff

Hydranencephaly: Observations on Transillumination of the Head of Infants
Eben Alexander Jr., Courtland H. Davis Jr., and Luke M. Kitahata

Relationship Between the Wernicke and the Korsakoff Syndrome
N. Malamud and S. A. Skillicorn

Early Ambulation and Psychotherapy for Treatment of Closed Head Injury
Ragnar Müller and Bengt Naumann

Lipoprotein Patterns of Spinal Fluid Obtained by Paper Electrophoresis
James K. Smith, Bruno Gerstl, William E. Davis, and Dorothy L. Orth

PSYCHIATRY SECTION

The Time Sense
William T. Lhamon and Sanford Goldstone

Glutathione Levels in Mental and Physical Illness
Sten Martens, Byron E. Leach, Robert G. Heath, and Matthew Cohen

DECEMBER 1956

VOLUME 76 NUMBER 6

Studies of the Role of Ceruloplasmin and Albumin in Adrenaline Metabolism
Byron E. Leach, Matthew Cohen, Robert G. Heath, and Sten Martens

Receptor Preferences in Schizophrenic Children
William Goldfarb

EEG During Electroconvulsive Therapy with Succinycholine
Thomas C. Piekenbrock, Robert C. Taylor, and Dorothy R. Becka

Discharge and Readmission Among Mental Hospital Patients
J. M. Wanklin, D. F. Fleming, Carol Buck, and G. E. Hobbs

Physiologic Stress Response Evaluation by Focused Interviewing
Sanford I. Cohen, Albert J. Silverman, and George Zuidema

Chlorpromazine and Hepatic Function
Vernon Kinross-Wright and John H. Moyer

Complete Contents First Inside Page

AMERICAN MEDICAL ASSOCIATION Publication

COLONIAL HALL

One of Fourteen units in "Cottage Plan"

For Nervous Disorders

Maintaining the highest standards since 1884, the Milwaukee Sanitarium Foundation continues to stand for all that is best in the contemporary care and treatment of nervous disorders.

Photographs and particulars sent on request.

Josef A. Kindwall, M.D.
Carroll W. Osgood, M.D.
William T. Kradwell, M.D.
Benjamin A. Ruskin, M.D.
Lewis Danziger, M.D.
James A. Alston, M.D.
Edward C. Schmidt, M.D.
Isaac J. Sarfatty, M.D.

★

Waldo W. Buss, Executive Director

Chicago Office—1509 Marshall Field Annex Bldg.
25 East Washington St.—Wednesday, 1-3 P.M.
Phone—Central 6-1162

MILWAUKEE SANITARIUM FOUNDATION, INC.

Wauwatosa Wisconsin

A.M.A.

Archives OF NEUROLOGY AND PSYCHIATRY

DECEMBER 1956

VOLUME 76 NUMBER 6

INDEX TO A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY
FOR THE PERIOD
JULY THROUGH DECEMBER, 1956

AMERICAN MEDICAL ASSOCIATION Publication

THIS INDEX consists of two parts: Author and Title Index and Subject Index. A Table of Contents is not included, and subscribers who want one in the bound volume should arrange to have the Table of Contents of each of the six issues of this volume included among the pages to be bound.

TABLE OF CONTENTS

VOLUME 76 DECEMBER 1956 NUMBER 6

NEUROLOGY SECTION

ORIGINAL ARTICLES

PAGE

Studies on Headache
Ernst Pichler, M.D.; Adrian M. Ostfeld, M.D.; Helén Goodell, B.S., and Harold G. Wolff, M.D., New York 571

Hydranencephaly: Observations on Transillumination of the Head of Infants
Eben Alexander Jr., M.D.; Courtland H. Davis Jr., M.D., and Luke M. Kitahata, M.D., Winston-Salem, N. C. 578

Relationship Between the Wernicke and the Korsakoff Syndrome
N. Malamud, M.D., and S. A. Skillicorn, M.D., San Francisco 585

Early Ambulation and Psychotherapy for Treatment of Closed Head Injury
Ragnar Müller, M.D., and Bengt Naumann, M.D., Stockholm 597

Lipoprotein Patterns of Spinal Fluid Obtained by Paper Electrophoresis
James K. Smith, M.D.; Bruno Gerstl, M.D.; William E. Davis, M.S., and Dorothy L. Orth, B.A., Oakland, Calif. 608

SOCIETY TRANSACTIONS

Boston Society of Psychiatry and Neurology 615
Philadelphia Neurological Society 621

PSYCHIATRY SECTION

ORIGINAL ARTICLES

The Time Sense
William T. Lhamon, M.D., and Sanford Goldstone, Ph.D., Houston, Texas 625

Glutathione Levels in Mental and Physical Illness
Sten Martens, M.D.; Byron E. Leach, Ph.D.; Robert G. Heath, M.D., and Matthew Cohen, New Orleans 630

Studies of the Role of Ceruloplasmin and Albumin in Adrenaline Metabolism
Byron E. Leach, Ph.D.; Matthew Cohen; Robert G. Heath, M.D., and Sten Martens, M.D., New Orleans 635

Receptor Preferences in Schizophrenic Children
William Goldfarb, M.D., Ph.D., New York 643

EEG During Electroconvulsive Therapy with Succinycholine
Thomas C. Piekenbrock, M.D.; Robert C. Taylor, and Dorothy R. Becka, Hines, Ill. 653

Discharge and Readmission Among Mental Hospital Patients
J. M. Wanklin, B.A.; D. F. Fleming, M.A.; Carol Buck, M.D., Ph.D., D.P.H., and G. E. Hobbs, M.D., M.P.H., London, Ont., Canada 660

Physiologic Stress Response Evaluation by Focused Interviewing
Capt. Sanford I. Cohen; Capt. Albert J. Silverman, and Capt. George Zuidema (MC), U.S.A.F. 670

Chlorpromazine and Hepatic Function
Vernon Kinross-Wright, M.D., and John H. Moyer, M.D., Houston, Texas 675

REGULAR DEPARTMENTS

Books 681

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 76 DECEMBER 1956 NUMBER 6

COPYRIGHT, 1956, BY THE AMERICAN MEDICAL ASSOCIATION

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

EDITORIAL BOARD

SECTION ON NEUROLOGY

HAROLD G. WOLFF, Chief Editor
525 East 68th Street, New York 21

BERNARD J. ALPERS, Philadelphia
CHARLES D. ARING, Cincinnati
PERCIVAL BAILEY, Chicago
DEREK E. DENNY-BROWN, Boston
WILDER PENFIELD, Contributing Member, Montreal

SECTION ON PSYCHIATRY

ROY R. GRINKER Sr., Chief Editor
Institute for Psychosomatic and Psychiatric Research
29th Street and Ellis Avenue, Chicago 16

STANLEY COBB, Boston
GEORGE E. GARDNER, Boston
M. RALPH KAUFMAN, New York
DOUGLASS W. ORR, Seattle
FREDERICK C. REDLICH, New Haven, Conn.
JOHN WHITEHORN, Baltimore

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

AMERICAN MEDICAL ASSOCIATION SCIENTIFIC PUBLICATIONS
A. M. A. Specialty Journals
Monthly

A. M. A. Archives of Internal Medicine. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.*

A. M. A. Archives of Dermatology. Herbert Rattner, M.D., Chief Editor, 104 S. Michigan Ave., Chicago. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.†

A. M. A. Archives of Ophthalmology. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.†

A. M. A. Archives of Surgery. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.‡

A. M. A. Journal of Diseases of Children. Robert B. Lawson, M.D., Chief Editor, 1000 N. W. 17th St., Miami 36, Fla. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.†

A. M. A. Archives of Pathology. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.*

A. M. A. Archives of Neurology and Psychiatry. Harold G. Wolff, M.D., Chief Editor, Neurology, 525 E. 68th St., New York 21; Roy R. Grinker Sr., M.D., Chief Editor, Psychiatry, Institute for Psychosomatic and Psychiatric Research, 29th St. and Ellis Ave., Chicago 16. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.50.‡

A. M. A. Archives of Otolaryngology. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.50.‡

A. M. A. Archives of Industrial Health. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.*

* Price to students, interns, and residents: $6.00 in U. S. & possessions.

† Price to students, interns, and residents: $7.00 in U. S. & possessions.

‡ Price to students, interns, and residents: $8.00 in U. S. & possessions.

The price for individual copies applies only to this and the previous calendar year. Back issues older than two years are available through Walter J. Johnson, Inc., 111 Fifth Avenue, New York 3. Future reprints of back issues will be available through Johnson Reprint Corporation, 111 Fifth Avenue, New York 3.

The Journal of the American Medical Association. Weekly. Annual Subscription Price: Domestic, $15.00. Canadian, $17.00. Foreign, $21.50. Price to students, interns, and residents: $9.00 in U. S. & possessions.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar Year, $25.00.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

3 NEW BOOKS For Neurologists and Psychiatrists

FUNDAMENTALS OF CLINICAL NEUROPHYSIOLOGY

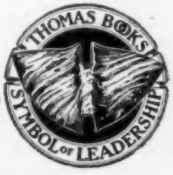
By **PAUL O. CHATFIELD, M.D.,** ***Chief, Section of Clinical Neurophysiology, National Institute of Neurological Diseases and Blindness.*** Written for medical students, trainees in neurology and psychiatry and technical personnel just entering the field. Many of the data presented here are unavailable except by recourse to the original papers on the various subjects treated. Special sections on 1) the nervous control of breathing; 2) electrophysiology of the spinal cord; 3) functional relationships of the cerebral cortex, thalamus, hypothalamus and limbic system. ***Published Fall '56, 384 pp., 225 il., Cloth, $8.50***

PRACTICAL PSYCHIATRY FOR INDUSTRIAL PHYSICIANS

By **W. DONALD ROSS, M.D.,** ***Associate Professor of Psychiatry, University of Cincinnati.*** Presents the principles and relevant details of the psychiatric aspects of the occupational physician's job of promoting mental and physical health in industry. Shows how to apply the methods which other experts have found to be effective. Features: many case examples, including individuals and groups. Includes: attitudes; basic techniques such as interviewing and examination; cooperation; detailed problems such as absenteeism and turnover. ***Published Fall '56, 404 pp., Cloth, $7.50***

SIX CHILDREN

By **ESTELLE J. FOOTE, M.D.,** ***Psychiatrist in Charge, Traveling School Clinic, Walter E. Fernald State School, Waverley, Massachusetts.*** An original, authoritative book written for those interested in helping children who are having any kind of trouble—and for those who want to keep children out of trouble in the first place. Based on complete studies and examinations of over 3600 children. Offers hundreds of pages of fresh, new material for studying, diagnosing and advising for them. ***Published Summer '56, 332 pp., Cloth, $5.50***



CHARLES C THOMAS • PUBLISHER
SPRINGFIELD • ILLINOIS

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. A carbon copy should be retained by the author. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than seventy characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given. To avert the possibility of legal action, patients' initials and hospital case numbers should not be published.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or $100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the $100 allowance. See an issue of this journal for examples. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins (or mountings) rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

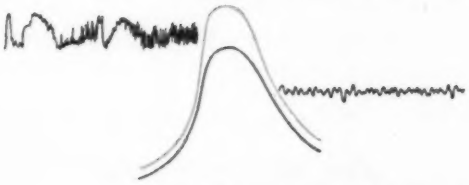
References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

"MYSOLINE" raises the convulsive threshold in grand mal and psychomotor attacks



"MYSOLINE," employed alone or in combination with other medication, controlled or markedly improved 73 per cent of 45 patients with major motor seizures. In each instance, the previous medication had proved to be ineffective.[1]

"MYSOLINE," when used as *initial therapy* in a series of 97 grand mal patients, controlled seizures in 57 per cent of the patients; an additional 22 per cent were improved.[2]

". . . after the proper dose was established, 'Mysoline' was well tolerated without [serious] side effects."[3]

1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

LITERATURE ON REQUEST

Supplied: Tablets, 0.25 Gm. Bottles of 100 and 1,000.

"MYSOLINE"®

Brand of Primidone

in epilepsy

Ayerst

AYERST LABORATORIES • New York, N. Y. • Montreal, Canada

5655

Ayerst Laboratories make "Mysoline" available in the United States by arrangement with Imperial Chemical (Pharmaceuticals) Limited.

relaxes both mind and muscle

for the average patient in everyday practice

- well suited for prolonged therapy
- well tolerated, nonaddictive, essentially nontoxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to chlorpromazine or reserpine
- does not produce significant depression
- orally effective within 30 minutes for a period of 6 hours

Indications: **anxiety and tension states, muscle spasm.**

THE ORIGINAL MEPROBAMATE®

Miltown

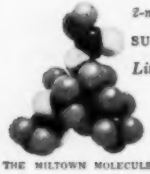
Tranquilizer with muscle-relaxant action

DISCOVERED AND INTRODUCED BY WALLACE LABORATORIES, *New Brunswick, N. J.*

2-methyl-2-n-propyl-1,3-propanediol dicarbamate—U.S. Patent 2,724,720

SUPPLIED: *400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.*

Literature and Samples Available on Request



THE MILTOWN MOLECULE

CM-3706-R2

Section on NEUROLOGY

Studies on Headache

Central versus Peripheral Action of Ergotamine Tartrate and Its Relevance to the Therapy of Migraine Headache

ERNST PICHLER, M.D.
ADRIAN M. OSTFELD, M.D.
HELEN GOODELL, B.S.
and
HAROLD G. WOLFF, M.D., New York

Earlier explanations of the mechanism of the action of ergotamine tartrate in ending migraine headache claimed a sedative effect mainly on the sympathetic nervous system.[1] The number of the bodily disturbances accompanying a migraine headache attack that could be attributed to autonomic overactivity were used as support for this view. Later, it was suggested that the cranial sympathetic nerves were implicated in the cranial vascular pain, and that their activity would be blocked by ergotamine tartrate. However, resection and division of the cervical sympathetic nerves supplying the cranial vessels failed to eliminate headache.[2]

In 1936 the dominant role of vasodilatation of the cranial vessels in the mechanism of migraine headache was demonstrated. It was shown that the administration of ergotamine tartrate was followed by a decrease in the amplitude of pulsations of the cranial arteries, mainly of the extracranial, with a concomitant reduction in intensity of the headache. Wolff, Hardy, and Goodell[4] also studied pain thresholds of the skin following the administration of ergotamine tartrate and demonstrated that it had no significant analgesic effect. Wolff and his associates inferred that the site of action was on the smooth muscle of the cranial arteries.

However, this view concerning the primary site of ergotamine tartrate has been challenged.[5] The question has been raised whether the effectiveness is due to a direct vasoconstrictor action on peripheral blood vessels or whether vasoconstriction occurs secondarily to a central action of the agent.

That ergotamine tartrate has significant central effects, as well as peripheral vasoconstrictor effects, in man[3] and animals* has been demonstrated.†

Its capacity to potentiate the analgesic action of certain agents and the "sedative effect" of the barbiturates has also been reported and summarized by Rothlin and Bircher,[7] Rothlin and Cerletti[5] have shown that ergotamine tartrate diminishes the pressor reflex in the cat, and Heymans and Régniers[11] have shown that the carotid sinus reflex is inhibited by ergotamine tartrate in amounts of 0.25 mg/kg. in cats. In the observations of von Euler and Schmiterlöw[12] ergotamine tartrate administered to cats in amounts of 0.1 mg. per kilogram of body weight inhibited selectively the carotid sinus pressor reflex elicited by lowering the intracarotid pressure, whereas the

Received for publication June 11, 1956.

Fulbright Research Fellow in Medicine (Neurology) from Graz, Austria (Dr. Pichler).

From the Departments of Medicine (Neurology) and Psychiatry, the New York Hospital-Cornell Medical College.

* References 5-6.

† References 7-10.

reflex could still be noted in response to chemical stimuli.

It is therefore of interest to establish whether the amount of ergotamine tartrate usually administered to humans in the therapy of migraine headache, approximately 0.007 mg. per kilogram of body weight,‡ has central effects pertinent to its action in terminating the migraine type of vascular headache. The purpose of the following investigations has been to ascertain whether ergotamine tartrate in the amounts usually given to migraine headache patients has a significant central effect in blocking or diminishing vasomotor reflexes.

Methods and Subjects

Eleven healthy and intact young men and, in addition, two patients with cervical sympathectomy and stellate ganglionectomy served as subjects. The carotid sinus reflex, the cold pressor response, and levarterenol-induced hypertension and bradycardia were used as indicators of possible central nervous system effects of ergotamine tartrate in three series of experiments. In a fourth series of experiments the effect of ergotamine tartrate on ostensibly sympathectomized cranial arteries was studied.

Throughout each experiment, the pulse waves of a branch of the superficial temporal artery were recorded at appropriate intervals, using a glycerin pelotte, a piezoelectric pulse-wave transducer, and a direct-writing Sanborn electrocardiograph. In the experiments involving the carotid sinus reflex the pulse rate was measured electrocardiographically for two minutes before, during, and for two minutes after pressure on the carotid sinus of one side. Manual pressure was applied for a period of 10 to 15 seconds.

Procedures and Results

SERIES I.—*Demonstration of Failure of Ergotamine Tartrate to Eliminate or Diminish the "Cold" Pressor Effect.*—Because the peripheral vasoconstriction and elevation of the blood pressure following immersion of a hand in ice water is mediated through central autonomic nervous activity, the cold pressor response was used to test the alleged central effects of ergotamine tartrate.

The pressor response to holding the hand in ice water (temperature 4 C) was recorded in six experiments before and after administration of ergotamine tartrate in five healthy, intact young male subjects.

Brachial artery systemic arterial blood pressures were measured by the sphygmomanometer, and temporal artery pulse waves were recorded at one- to three-minute intervals throughout the experiment by the device described above. After a control observation period of 20 minutes, the right hand and forearm were immersed in ice water for five minutes. The peripheral vasoconstriction was manifested by elevation of the blood pressure and by decrease in the amplitude of temporal artery pulsations of as much as 80%.

When, after the arm was removed from the ice water, the blood pressure and temporal artery pulsations had returned to initial levels, 0.5 mg. of ergotamine tartrate was administered intravenously. Within one to four minutes a decrease in the amplitude of pulsations of the temporal artery was evident. This proceeded to a maximum decrease of 50% to 80% within 5 to 20 minutes. Such decreased amplitude of pulsations persisted for one to two hours. All subjects experienced a minor degree of nausea, which began 20 to 30 minutes after the injection, when vasoconstriction had already been maximal for 15 or more minutes, and lasted approximately 30 minutes. Fifteen to twenty minutes following the administration of the ergotamine, when a maximal reduction in amplitude of the temporal artery pulsations of 50%-80% was apparent, the hand and forearm were again immersed in ice water for five minutes, and blood pressure was recorded at one-minute intervals. This procedure was repeated 50 to 70 minutes following administration of the ergotamine tartrate. In each of the five subjects there was a rise in blood pressure equivalent in magnitude to that effected by the cold before the administration of the agent. Also, after ergotamine tartrate, immersion of the hand in ice water induced a further decrease in the amplitude of tem-

‡ References 2-3.

poral artery pulsation, but since the latter had already been reduced greatly by ergotamine, the percentage change was not easily measured. Although the nausea experienced by each subject was evidence of a central action of the agent, it was clearly demonstrated that ergotamine tartrate did not block or appreciably modify the cold pressor response in these five subjects.

SERIES II.—*Demonstration of Failure of Ergotamine Tartrate to Alter the Magnitude of the Carotid Sinus Reflex.*—The effect of ergotamine tartrate on the carotid sinus reflex, another centrally mediated response involving slowing of the pulse rate, was studied in eight experiments on five healthy intact male subjects. In addition to readings of the blood pressure and measurements of the amplitude of superficial temporal artery pulsations, the pulse rate was recorded electrocardiographically before, during, and after manual pressure on the carotid sinus. Two, three, or four carotid sinus responses were elicited in this way during the control period at approximately two- to eight-minute intervals.

The slowing of the pulse rate was evident mainly in the first five heart beats during pressure on the carotid sinus. Hence, the average of the first five R-R distances in the electrocardiogram, beginning with the onset of the pressure on the carotid sinus, was compared with the average of comparable periods before and after the effects of the pressure had ended.

After the administration of 0.5 mg. of ergotamine tartrate, and when the vasoconstrictor effect on the temporal artery had become evident in decreased amplitude of pulsations and when the subjects were experiencing nausea, carotid sinus pressure evoked responses, identical with those elicited before the administration of the agent.

SERIES III.—*Demonstration of Failure of the Agent Hydergine to Block the Peripheral Vasoconstrictor Effect or to Facilitate the Central Action of Ergotamine Tartrate.*—Hydergine is an equiproportional mixture of 0.1 mg. of each of the methanesulfonates of three dihydrogenated ergot alkaloids, dihydroergocornine, dihydroergokryptine, and dihydroergocristine.

A combination of Hydergine and ergotamine tartrate was used for the following reasons: Hydergine inhibits the vasomotor center, on the one hand, as shown by Konzett and Rothlin,[13] and, on the other, it has a peripheral vasodilator action, as demonstrated by Barcroft, Konzett, and Swan,[14] and is without notable effect on the intensity of migraine headache.[6]

The procedure described in Series II, using the carotid sinus reflex as an indicator of central nervous activity, was repeated but was varied to include observations on the effects of Hydergine on the possible central and peripheral effects of ergotamine tartrate in three experiments. In two of these experiments 0.3 mg. of Hydergine was given intramuscularly at 21 and 22 minutes, respectively, after 0.5 mg. of ergotamine tartrate had been administered intravenously, and when the vasoconstrictor effect on the temporal artery was conspicuous. In the third experiment 0.5 mg. of ergotamine tartrate was administered 32 minutes after the intravenous injection of 0.3 mg. of Hydergine. In spite of the alleged vasodilator effect of the Hydergine, the vasoconstrictor action of the ergotamine tartrate was not blocked. Within a few minutes of administration of the latter agent, a marked decrease in amplitude of pulsations of the temporal arteries became apparent. In all three experiments the pulse rate slowed in response to carotid sinus pressure, as it did in control observations and after ergotamine tartrate alone. The results of this experiment are shown graphically in Figure 1.

Comment

In each subject to whom ergotamine tartrate was administered in these experiments a reduction in the amplitude of pulsation of the temporal artery often began within one minute after administration of the agent, and a reduction of as much as 50% frequently occurred within two to five

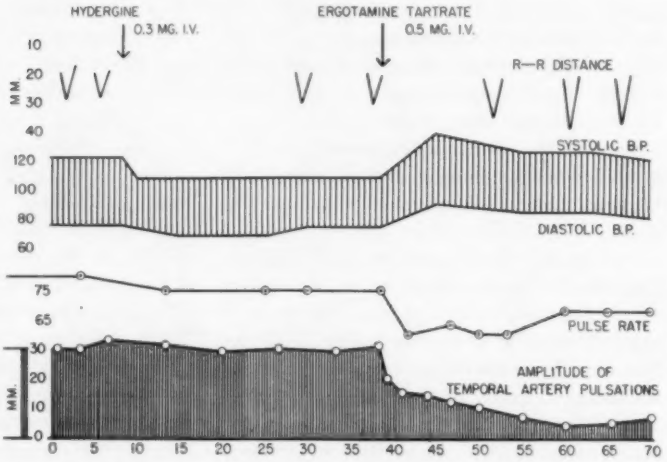


Fig. 1.—Demonstration of the failure of Hydergine to block the peripheral vasoconstrictor action of ergotamine tartrate, and of the failure of ergotamine tartrate to block the effect of pressure on the carotid sinus in slowing the pulse rate.

minutes. The administration of the given amounts of Hydergine did not significantly change the amplitude of temporal artery pulsations, whether it was administered before or after ergotamine tartrate. Also, it did not alter the effectiveness of ergotamine tartrate in diminishing the amplitude of temporal artery pulsations or diminish the feelings of nausea.

The effect of pressure on the carotid sinus in slowing the pulse rate was not blocked by the administration of the given amount of ergotamine tartrate. In addition, the administration of the vasodilator agents contained in Hydergine both before and after the administration of ergotamine tartrate did not alter the magnitude of the carotid sinus reflex. All of these results indicate that the peripheral vasoconstrictor action of ergotamine tartrate on the temporal artery occurs independently of any demonstrable central action on the vasomotor centers.

SERIES IV.—*Demonstration of Ineffectiveness of Ergotamine Tartrate in Altering Levarterenol-Induced Vagal Bradycardia.*—When levarterenol is administered intravenously in amounts sufficient to elevate the blood pressure, there is mediated through the carotid and aortic pressor receptors, medullary cardioinhibitor centers, and the vagi a significant slowing of the pulse. It would seem possible, if ergotamine tartrate in the usual therapeutic amount has a central action, that such levarterenol-induced bradycardia might be blocked following the administration of ergotamine tartrate. Therefore six healthy young men served as subjects in six experiments to ascertain whether ergotamine tartrate prevents the bradycardia elicited through the vagal action of levarterenol.

Four cubic centimeters of 0.1% solution of levarterenol in 500 cc. of 5% dextrose in water (containing 0.008 mg. of levarterenol per cubic centimeter) was infused intravenously at a rate sufficient to raise the systolic blood pressure 20 to 30 mm. Hg and to slow the pulse rate by approximately 10 to 20 beats per minute. The infusion at a rate of 10 to 15 drops per minute, or of approximately 0.005 mg. of levarterenol per minute, was continued for 5 to 10 minutes. The infusion experiment was repeated again 15 minutes after the intravenous administration of 0.5 mg. of ergotamine tartrate; in two instances the levarterenol was again administered at 50 to 60 minutes after the ergotamine tartrate administration. However, the electrocardiograms recorded throughout the experiment showed no significant difference between the bradycardia elicited by levarterenol during control periods and that elicited during the periods of effective action of ergotamine tartrate (Fig. 2).

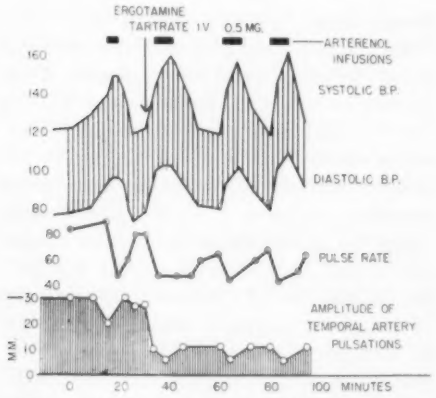


Fig. 2.—Demonstration of the ineffectiveness of ergotamine tartrate in blocking levarterenol-induced bradycardia.

SERIES V.—*Demonstration of Persistence of the Peripheral Vasoconstrictor Effect of Ergotamine Tartrate Following Cervical Sympathectomy.*—To ascertain whether ergotamine tartrate is effective in reducing the amplitude of pulsations of temporal arteries denervated by cervical sympathectomy, three experiments on two patients were performed.

The first subject was a woman aged 54. On Jan. 20, 1954, right cervical sympathectomy, and on Feb. 9, 1954, left stellate ganglionectomy, had been performed (at the New York Hospital, by Dr. Bronson Ray). After each of these procedures a Horner syndrome appeared on the involved side and the hand on this side was warm. The Horner syndrome was clearly in evidence when these observations were made, on Aug. 30, 1955, and as well a starch-iodine test showed absence of facial sweating, whereas profuse sweating occurred over the rest of the face and body.

In the first observation pulsations were recorded from the left temporal artery, i. e., from the side of the stellate ganglionectomy. One week later, in a second observation, pulsations were recorded from the right temporal artery, i. e., on the side of the cervical sympathectomy. Pulsations were first recorded during a control period. Ergotamine tartrate, 0.3 mg. in the first and 0.5 mg. in the second experiment, was administered intravenously. During the ensuing hour in each of the two observations records of temporal artery pulsations were made at one- to two-minute intervals.

Similar studies were made in another woman, aged 36, who had undergone a bilateral stellate ganglionectomy (Oct. 6, 1952, on the right side and Oct. 9, 1952, on the left side). A bilateral Horner syndrome was evident on the day of this experiment, in September, 1955.

The decrease in amplitude of pulsations of the temporal artery following ergotamine tartrate was neither retarded nor diminished as compared with its effects in intact subjects. Also, there was no difference in degree of effect on the side of the stellate ganglionectomy as compared with that on the side of the cervical sympathectomy. Thus, in these two subjects with ostensibly sympathectomized extracranial arteries, the vasoconstrictor action of ergotamine tartrate was as effective as in intact control subjects.

General Comment

No evidence has been obtained in the experiments described to indicate a predictable decrease of magnitude of the carotid sinus reflex in healthy young male subjects following the administration of ergotamine tartrate in the usual therapeutic amounts of 0.5 mg. intravenously. The vasomotor response in the cold pressor test was likewise unaltered after ergotamine tartrate administration. Thus, when the hand was held in ice water at 4 C following the administration of ergotamine, the pulse rate increase, blood pressure elevation, and decrease in the amplitude of temporal artery pulsations were of a magnitude comparable to that in control tests before ergotamine tartrate. This indicates that the amount of ergotamine tartrate sufficient for temporal artery constriction and the therapeutic effects in migraine headache is less than the amount necessary for evoking the central effects shown by Rothlin and Cerletti.[16]

The magnitude of the carotid sinus reflex is not significantly changed by Hydergine in the amount used (i. e., 0.3 mg., i. v.). Nor does its vasodilator action prevent the vasoconstrictor effect of ergotamine tartrate or cause a significant dilatation of cranial vessels already constricted by ergotamine.

Von Euler and Schmiterlöw [12] showed that the pressor response to carotid occlusion in cats was eliminated after the administration of ergotamine tartrate in amounts of 0.1 mg. per kilogram. In these experiments in humans, however, intravenous administration of ergotamine tartrate in amounts of 0.5 mg. to adult male subjects weighing from 65 to 85 kg. did not prevent the bradycardia effected by stimulation of the carotid sinus.

In these subjects there were bradycardia and an elevation of blood pressure during an infusion of levarterenol both before and after the administration of ergotamine tartrate. Therefore, it must be concluded that the bradycardia reflexly induced by the rise of blood pressure during infusion of levarterenol is not blocked, nor indeed altered, by ergotamine tartrate in the amounts administered for a therapeutic purpose.

Also, the vasoconstriction, as exhibited in the decreased amplitude of pulsations of the temporal artery caused by levarterenol or by immersing the hand in ice water, has not been inhibited by ergotamine tartrate in these human subjects. On the contrary, the vasoconstriction already induced by ergotamine tartrate was enhanced in response both to cold and to levarterenol.

Although in the present investigation ergotamine tartrate, in the amounts used and sufficient to induce temporal artery constriction, did not block the carotid sinus reflex, the pressor response in the cold pressor test, or the bradycardia caused by elevation of blood pressure during levarterenol infusion, it is possible that larger amounts of ergotamine tartrate would exhibit a central effect.

However, as regards the effectiveness of ergotamine tartrate in terminating the migraine headache attack, a variety of evidence points away from its central action and indisputably toward its direct vasoconstrictor action on extracranial blood vessels. Thus, Hydergine has been shown to have a lively central effect in laboratory animals. It exerts a marked inhibitory action on psychomotor functions in waltzing mice [16]; on autonomic reflexes, i. e., the carotid sinus reflex [6] in laboratory animals, and a marked inhibition of psychomotor activity in man,[17] but has no effect in diminishing the intensity of pain in a migraine attack.[15] This lack of therapeutic effect of Hydergine in migraine can be attributed to the main difference in its pharmacological action as compared with that of ergotamine tartrate; i. e., Hydergine, with a lively central effect, weakly dilates the cranial blood vessels, whereas ergotamine constricts them.

The conclusion that the vasoconstriction following ergotamine tartrate is effected peripherally is supported by the observations of prompt and striking decrease in the amplitude of temporal artery pulsations following its administration in the sympathectomized patients described above. It is also supported by the observations of Pichler, Lazarini, and Filippi [18] that cranial artery vasoconstriction occurs in vitro when such arteries are suspended in a solution of ergotamine tartrate. That peripheral vasoconstriction of the cranial arteries is the mechanism through which ergotamine tartrate terminates the migraine attack is also supported by the observations that other vasoconstrictor agents may terminate migraine headache.§

Summary

Experimental evidence of a prompt and striking peripheral vasoconstrictor action, together with evidence indicating a lack of central action of ergotamine tartrate in causing such vasoconstriction in human subjects, has been adduced.

After the intravenous administration of ergotamine tartrate, marked peripheral vasoconstriction preceded sensations of nausea by 15 or more minutes.

§ References 2, 3, 19, 20.

After the administration of ergotamine tartrate, elevation of the blood pressure during the "cold pressor" reaction was not prevented.

The sensitivity of the carotid sinus reflex was not altered even during the period of nausea following administration of ergotamine tartrate.

Bradycardia during infusion of levarterenol occurred as predictably after the administration of ergotamine tartrate as before.

The administration of Hydergine (three dihydrogenated ergot alkaloids) either before or after the administration of ergotamine tartrate did not alter the vasoconstrictor effect of the latter agent.

In two subjects with ostensibly sympathectomized extracranial arteries, the peripheral vasoconstrictor action of ergotamine tartrate was as effective as in intact subjects.

Conclusion

It is concluded that in terminating a migraine headache attack the effective action of ergotamine tartrate is peripheral, and that in such action as that elicited by the therapeutic amounts administered to human subjects central effects are not significant.

REFERENCES

1. Maier, H. W.: L'ergotamine, inhibiteur du sympathique étudié en clinique, comme moyen d'exploration et comme agent thérapeutic, Rev. neurol. 33:1104, 1926.

2. Wolff, H. G.: Headache and Other Head Pain, London, Oxford University Press, 1948.

3. Graham, J. R., and Wolff, H. G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, A. Res. Nerv. & Ment. Dis., Proc. 18:638, 1937.

4. Wolff, H. G.; Hardy, J. D., and Goodell, H.: Measurement of the Effect on the Pain Threshold of Acetylsalicylic Acid, Acetanilid, Acetophenetidin, Aminopyrine, Ethyl Alcohol, Trichlorethylene, a Barbiturate, Quinine, Ergotamine Tartrate and Caffeine: An Analysis of Their Relation to the Pain Experience, J. Clin. Invest. 20:63, 1941.

5. Rothlin, E., and Cerletti, A.: Untersuchungen über die Kreislaufwirkung des Ergotamin, Helvet. physiol. et pharmacol. acta 7:333, 1949.

6. Rothlin, E.: Recherches expérimentales sur l'ergotamine, alcaloïde spécifique de l'ergot de seigle, Arch. internat. pharmacodyn. 27:459, 1923.

7. Rothlin, E., and Bircher, R.: Allergy: The Autonomic Nervous System and Ergot Alkaloids, Progr. Allergy 3:434, 1952.

8. Tietze, E. B.: Mode of Action of Ergotamine Tartrate in Psychotic Patients, Psychiat. Quart. 14:481, 1940.

9. Heath, R. G., and Powdermaker, F.: Use of Ergotamine Tartrate as Remedy for "Battle Reaction," J. A. M. A. 125:111, 1944.

10. Lemkau, P. V., and Sampliner, R. B.: Ergotamine Tartrate in Treatment of Combat Exhaustion, Arch. Neurol. & Psychiat. 60:61, 1948.

11. Heymans, C., and Régniers, P.: Influence de l'ergotamine sur les reflexes cardio-vasculaires du sinus carotidien, Arch. internat. pharmacodyn. 36:116, 1929.

12. von Euler, U. S., and Schmiterlöw, C. G.: The Action of Ergotamine on the Chemical and Mechanical Reflexes from the Carotid Sinus Region, Acta physiol. scandinav. 8:122, 1944.

13. Konzett, H., and Rothlin, E.: Investigations on the Hypotensive Effect of the Hydrogenated Ergot Alkaloids, Brit. J. Pharmacol. 8:20, 1953.

14. Barcroft, H.; Konzett, H., and Swan, H. J. C.: Observations on the Action of the Hydrogenated Alkaloids of the Ergotoxine Group on the Circulation in Man, J. Physiol. 112:273, 1951.

15. Friedman, A. P., and von Storch, T. C.: Recent Advances in Treatment of Migraine, J. A. M. A. 145:1325, 1951.

16. Rothlin, E., and Cerletti, A.: Über einige pharmakologische Untersuchungen an Mäusen mit congenitaler Drehsucht, Helvet. physiol. et pharmacol. acta 10:319, 1952.

17. Solms, H.: Psychosedativer Effekt der Sekale-Alkaloide (DHE 45, DHO 180 and Hydergin) auf psychomotorisch Erregte, Schweiz. Arch. Neurol. u. Psychiat. 68:64, 1951.

18. Pichler, E.; Lazarini, W., and Filippi, R.: Über schraubenförmige Struktur von Arterien, Arch. exper. Path. u. Pharmakol. 219:420, 1953.

19. Pichler, E.: Der Kopfschmerz, Wien, Springer-Verlag, 1952.

20. Ostfeld, A. M., and Wolff, H. G.: Arterenol (Norepinephrine) and Vascular Headache of the Migraine Type, A. M. A. Arch. Neurol. & Psychiat. 74:131, 1955.

Hydranencephaly: Observations on Transillumination of the Head of Infants

EBEN ALEXANDER Jr., M.D.
COURTLAND H. DAVIS Jr., M.D.
and
LUKE M. KITAHATA, M.D., Winston-Salem, N. C.

The technique of observing light shining through the head of an infant is not new, but in view of its value as a diagnostic method and as a prognostic sign, if positive, it has been neglected by neurologists and pediatricians. In 1831 Richard Bright[1] described the case of James Cardinal: "If a candle was held behind his head or the sun happened to be behind it, the cranium appeared semitransparent; and this was more or less evident until he obtained his fourteenth year." This person, with a grossly enlarged head, lived to the age of 29, walked at the age of 6 years for the first time, and, in fact, learned to read and write. He was, however, obviously retarded and suffered from epileptic seizures. The autopsy, beautifully illustrated in Bright's text, disclosed a huge cranium filled with clear fluid and only a vestigial cortex present at the base of a huge cavity.

This case is unusual in many ways, not only in the accurate observations of Sir Richard Bright, but also in the age to which the patient survived and the degree to which he could learn in spite of obviously severe brain deficiency. Cruveilhier * termed this condition "hydroanencephaly." Hamby, Krauss, and Beswick,[3] who made very astute observations on seven cases, used the term hydranencephaly.

There have been several other valuable contributions to the understanding of this subject, incuding those of Yakovlev and Wadsworth,† Cohn and Neumann,[6] Watson,[7] and Poser, Walsh, and Scheinberg.[8] The cause of hydranencephaly is unknown, though it is certainly a congenital developmental disorder. Since some patients have neither enlargement of the head nor increased intracranial pressure, the development of the process does not depend alone on increased intraventricular pressure. All would agree that it is a serious developmental defect with a poor prognosis, and the data to be presented will further substantiate this.

Transmission of light through the head depends on several physical factors. The collection of clear or yellow fluid in the cranium and the relative absence of cerebral cortex seem to be prerequisites of transillumination, although the head of a child so affected may not be grossly enlarged (Fig. 1). The relative thickness of the infant's skull, at least up to one year, seems to be of little importance.

The light source is of obvious significance, and certain standards have been assumed. For diagnosis on the wards and in the clinic, a darkened closet is utilized in which the examiner has accommodated his eyes to darkness for three minutes. The light source is an ordinary hand flashlight containing two standard batteries. In some patients with no cerebral or cerebellar cortex, transillumination may be evident in the usual indoor light with the use of even a small pencil-type flashlight (Figs. 2 and 3). Grossly

Received for publication May 2, 1956.
Presented at the Southern Neurosurgical Society, Jacksonville, Fla., March 24, 1956.

From the Section of Neurosurgery, Department of Surgery, of the Bowman Gray School of Medicine of Wake Forest College.

* Cruveilhier,[2] cited by Hamby, Krauss, and Beswick.[3]

† References 4 and 5.

Fig. 1.—Eleven-month-old boy. Left, photograph of infant; right, transillumination photograph. Note lack of head enlargement.

bloody fluid within the cranial cavity will retard transmission of light, but it has been observed that yellow fluid within the cranium, containing as much as 300 mg. of protein per cubic centimeter, does not impede transillumination of light. In the infant's head with no cerebral cortex and with clear fluid, there is clear transillumination, with very prominent visualization of the major venous channels in the head, particularly the venous sinuses (Fig. 4). Transmission of light may be discovered to be generalized, more prominent on one side of the supratentorial region than on the other (Fig. 1), limited to one quadrant of the head, or, as in one case in our group, strictly localized to the infratentorial region (Fig. 5).

A specific attempt has been made to determine how much cortex is required to cast a significant shadow in transillumination. Those patients with no cortex whatever, of course, transmit light freely. Five infants with moderate degrees of internal

Fig. 2.—Four-month-old girl. Left, photograph of child; right, transillumination of head. Light is visible through eyes.

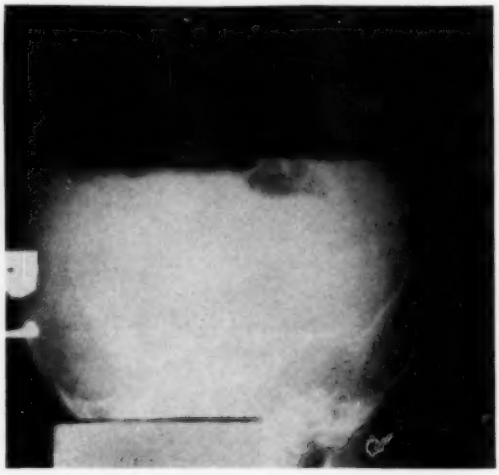


Fig. 3.—Same patient as that in Figure 2. Skull film after injection of air by puncture through cornal suture. Film taken in sitting position with horizontal roentgen beam.

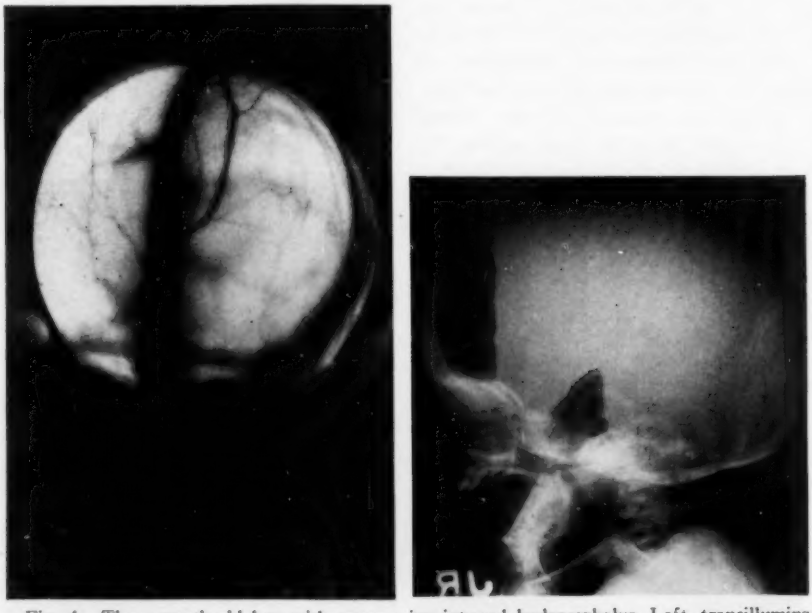


Fig. 4.—Three-month-old boy with progressive internal hydrocephalus. Left, transillumination of head. Sagittal sinus and veins of scalp show clearly. Right, ventriculogram showing air in both lateral ventricles; brow up; horizontal beam. Cortex less than 1 cm. in thickness.

hydrocephalus were subjected to the transillumination test, all of them with the usual flashlight and also with an extremely bright Photoflood bulb, ordinarily used in photography. In none of these patients with a cortical mantle of 1 cm. in thickness or greater was there any transmission of light. In each patient the thickness of the cortex was accurately determined by air study combined with horizontal-beam x-rays (Fig. 6).

Fig. 5.—Four-month-old boy. Hydrocephalus due to atresia of the foramina of Luschka and Magendie. Light transilluminates infratentorial region freely but does not show in supratentorial region, in which cortex measured about 2 cm.

There were all degrees of transillumination. A cortical mantle 2 to 3 mm. in thickness adjacent to the dura in the vault of the skull did not prevent light shining through. Some patients showed passage of light through most portions of the head except for a localized area in which there was obvious sparing of residual cortex.

For purposes of illustration, a convenient apparatus has been devised by the Department of Medical Illustration for photographing the process of transillumination, either on color film or on black and white film.[9] All the illustrations used were made with this type of apparatus, in various stages of its development.

Case Material

The material for study of these cases was based on 20 patients. Two of these patients were investigated before 1953 and were not subjected to transillumination but were found to have complete absence of cortex, confirmed at craniotomy. They were entirely similar to those patients accurately described by Hamby, Krauss, and Beswick.[3] The other 18 cases have been collected over the past two years; one of these showed transmission of light only in the infratentorial region, and was subsequently proved to have blockage at the foramina of Luschka and Magendie, with a very atrophic cerebellum. The other 17 cases showed either generalized or localized transmission of light in the supratentorial region.

Of these 17 patients, 7 had additional studies, including the so-called Dandy neutral phenolsulfonphthalein dye test. In all seven of these patients there was evidence of obstruction to the flow of cerebrospinal fluid. Only one patient showed passage of a small amount of dye from the ventricles

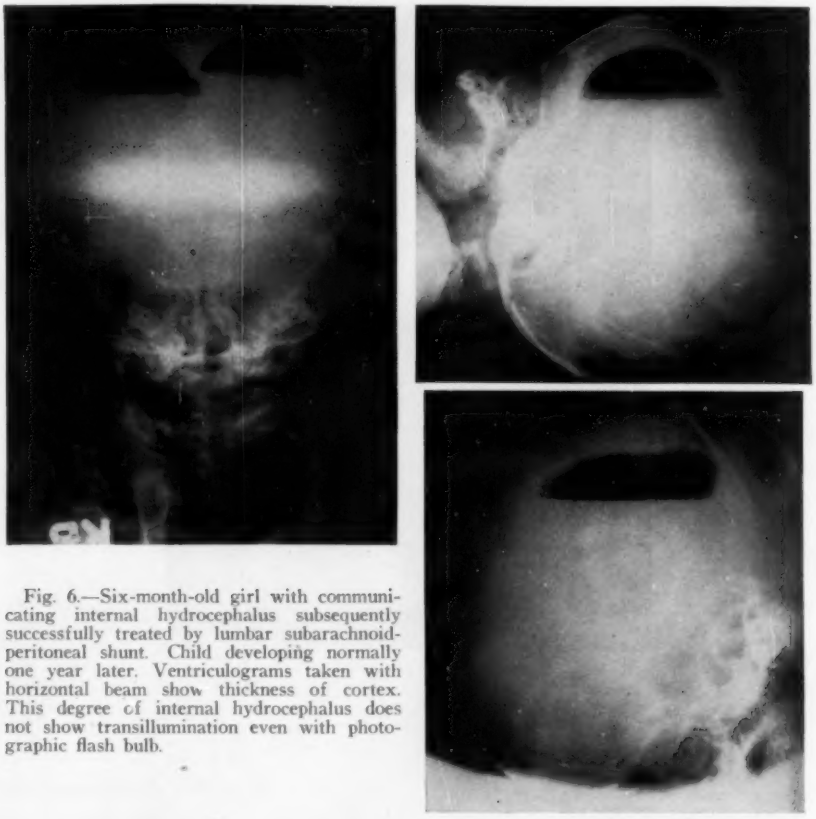


Fig. 6.—Six-month-old girl with communicating internal hydrocephalus subsequently successfully treated by lumbar subarachnoid-peritoneal shunt. Child developing normally one year later. Ventriculograms taken with horizontal beam show thickness of cortex. This degree of internal hydrocephalus does not show transillumination even with photographic flash bulb.

into the lumbar subarachnoid space, in 16 minutes; the others showed no passage of dye in 30 minutes or more. This finding is in accord with postmortem studies of patients of this type, almost all of whom have shown absence or stenosis of the aqueduct of Sylvius.[5]

It is well known that newborn babies and infants up to the age of 2 months require no cerebral cortex in order to behave in a manner considered normal for this age. Hamby, Krauss, and Beswick [8] reported one patient approved for adoption at one week of age who was later found to have hydranencephaly. Thirteen of the seventeen patients observed in this series with transmission of light in the supratentorial region had some degree of hydrocephalus at the time of initial examination. In four others the head either was not enlarged or was only 2 or 3 cm. larger than the chest in measurement of the circumference.

Without exception in this group of cases, retardation of motor and mental development became increasingly apparent in the children who survived. This applied to the patients who had localized areas of transillumination, as well as those in whom the transillumination was generalized. Twelve of the children are surviving at the present time, at ages of 6 to 26 months. Of the eight infants with transmission of light through the head or absence of the cortex (including those observed at operation), the average length of life was five and one-half months.

The oldest surviving child is now 26 months of age, extremely spastic, and obvi-

ously severely retarded. His parents, who have devoted amost full time to him, say that he occasionally utters single words. His motor development, however, including the ability to reach for objects, to turn over, and to hold up his head, is severely retarded. None of the surviving children have learned to sit alone or to stand. Six of the infants have had overt convulsive seizures. Four of these were over 10 months of age, suggesting that a higher percentage of these children would have had convulsive seizures had they been observed over a longer period of time.

Electroencephalograms were performed on most of the patients studied, and these findings will be made the basis of a separate report. Such studies have previously been carried out by Hamby [3] and Poser [8] and their associates. In general, when there is complete absence of cortex, as one might anticipate, there is complete absence of electrical activity in that portion of the skull.

Summary

Transillumination of the head of infants is a useful diagnostic tool and is extremely useful for prognosis.

The material for study of transillumination has been based on 20 cases observed over the last few years. Seventeen of these showed transmission of light above the tentorium and one below the tentorium, and two were investigated by craniotomy but were not subjected to transillumination.

Most of the children showed enlargement of the head, but four had relatively normal-sized heads, and in these the transillumination was as clear as in those with enlarged heads.

Transmission of light through the head may become increasingly apparent as the cortical mantle becomes thinned out in progressive hydrocephalus. The ability to transmit light depends on clear or clear yellow cerebrospinal fluid and the absence, or almost complete absence, of the cortical mantle. A cortical mantle of 1 cm. will prevent transillumination, but a mantle of 2 or 3 mm. will allow light to pass through.

The prognosis for all children observed, whether the transillumination was localized or generalized, was extremely poor, and none of these children has developed in a normal fashion. Eight died at an average age of 5½ months; the ages of the other survivors ranged from 6 to 26 months. The highest grade of development reached is that of a patient who says an occasional single word, but he is unable to hold up his head, reach for objects, or behave in a normal fashion.

A simple apparatus for recording of transmission of light through the head on photographic film has been devised.

Addendum

Dr. A. Price Heusner, neurosurgeon of the Memorial Hospital, Chapel Hill, N. C., in a valuable discussion of this paper when it was presented before the Southern Neurosurgical Society, Jacksonville, Fla., called our attention to papers published by von Bokay on this subject. The last of these papers [10] summarizes all of his previous observations and publications. Von Bokay had seen altogether 37 cases, and his general experience was the same as that reported in the paper on transillumination given above. He apparently had not devised any special method for permanent recording of such transillumination on photographs.

REFERENCES

1. Bright, R.: Diseases of the Brain and Nervous System, in Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy, London, Longman, Rees, Orme, Brown, and Green, Paternoster-Row, and S. Highley, 1831, Vol. 2, Case CCV, pp. 431-435.

2. Cruveilhier, J.: Anatomie pathologique du corps humain, Paris, J. B. Ballière, 1829-1835, Vol. 1, Bk. 15, p. 2, Plate 4.

3. Hamby, W. B.; Krauss, R. F., and Beswick, W. F.: Hydranencephaly; Clinical Diagnosis; Presentation of 7 Cases, Pediatrics 6:371-383, 1950.

4. Yakovlev, P., and Wadsworth, R. C.: Schizencephalies; a Study of the Congenital Clefts

in the Cerebral Mantle: I. Clefts with Fused Lips, J. Neuropath. & Exper. Neurol. 5:116-130, 1946.

5. Yakovlev, P., and Wadsworth, R. C.: Schizencephalies; a Study of the Congenital Clefts in the Cerebral Mantle: II. Clefts with Hydrocephalus and Lips Separated, J. Neuropath. & Exper. Neurol. 5:169-206, 1946.

6. Cohn, R., and Neumann, M. A.: Porencephaly: A Clinicopathologic Study, J. Neuropath. & Exper. Neurol. 5:257-270, 1946.

7. Watson, E. H.: Hydranencephaly: Report of 2 Cases Which Combine Features of Hydrocephalus and Anencephaly, Am. J. Dis. Child. 67: 282-287, 1944.

8. Poser, C. M.; Walsh, F. C., and Scheinberg, L. C.: Hydranencephaly: Case Report, Neurology 5:284-289, 1955.

9. Taylor, L.; Dent, J.; Lynch, G., and Alexander, E., Jr.: An Apparatus for Photography of Transillumination of the Head, J. Neurosurg. 13:219-220, 1956.

10. von Bokay, J.: Über den Wert der Transparenz-Untersuchungen bei Hydrocephalus internus congenitus, Acta pædiat. 13:48-52, 1932.

Relationship Between the Wernicke and the Korsakoff Syndrome

A Clinicopathologic Study of Seventy Cases

N. MALAMUD, M.D.
and
S. A. SKILLICORN, M.D., San Francisco

It has been suggested in the literature from time to time that Wernicke's and Korsakoff's syndromes may be related.

"Acute hemorrhagic polioencephalitis superior" has been firmly established as a distinct clinical and pathologic entity since its original description, in 1881, by Wernicke.[1] The characteristic picture of ophthalmoplegia, ataxia, confusional mental state, and often peripheral neuritis, occurring predominantly in alcoholic patients, and the necropsy findings of acute hemorrhagic lesions in the periventricular and periaqueductal areas of the thalamus, hypothalamus, and brain stem are well known.

Korsakoff's psychosis, originally described in 1887,[2] characterized by memory impairment, temporal disorientation, and confabulation, with or without peripheral neuritis, also occurs most frequently in alcoholic patients. Athough this syndrome is more prevalent than Wernicke's form, it is clinically less specific and has not been defined adequately from a neuropathologic viewpoint.

The purpose of the present study is to determine, if possible, the validity of the suggestion that there is a relationship between the two syndromes and to establish, on the basis of a large series of cases, the neuropathology of Korsakoff's psychosis.

Received for publication April 23, 1956.

From the Laboratory of Neuropathology, Langley Porter Clinic, and the Department of Neurology, University of California School of Medicine.

Method

A thorough review was made of 70 patients who showed the clinical picture of Korsakoff's psychosis. The case studies were collected over a 10-year period, from 1946 to 1956. The patients had been committed to various mental hospitals in the State of California, where the clinical evaluations and general autopsies were performed. All the brains were studied in the laboratory of neuropathology at the Langley Porter Clinic.

Gross and histologic examinations of the central nervous system were done in each of the 70 cases. Multiple sections of the brain were obtained for microscopic evaluation from representative areas of the cerebral cortex; from the thalamus, hypothalamus, basal ganglia, various levels of the midbrain, pons, and medulla, and from the cerebellum. Study of the spinal cord was incomplete, since only the high cervical portions were available in 12 cases.

Staining methods employed included hematoxylin and eosin, the Nissl and the von Braunmühl (modification of Bielschowsky) neuronal stains, the Holzer glial stain, the Weil myelin sheath stain, and the hematoxylin-Van Gieson and Laidlaw connective tissue stains.

Results

Clinical Features (Table 1).—There were 52 (74%) males and 18 (26%) females. Severe chronic alcoholism was confirmed in 63 cases (90%); the remaining 7 patients (10%) were nonalcoholics but showed prolonged malnourishment, which in 4 of them was associated with carcinoma of the gastrointestinal tract. All patients had been committed to institutional care because of mental deterioration, which was characterized by impairment of memory in every case (100%) and associated with disorientation for time in 66 cases (94%). Confabulation was described in 23 (33%). Nineteen (27%) exhibited paranoid delusional features, and nine (13%) had hallucinations.

TABLE 1.—*Clinical Aspects of Seventy Cases of Korsakoff's Syndrome*

	Incidence
Males	52 (74%)
Females	18 (26%)
Chronic alcoholism	63 (90%)
Nonalcoholics (four with gastrointestinal carcinoma)	7 (10%)
"Mental deterioration"	70 (100%)
Memory impairment	70 (100%)
Disorientation and confusion	66 (94%)
Confabulation	23 (33%)
Paranoid delusions	19 (27%)
Hallucinations	9 (13%)
Convulsive seizures	5 (7%)
Average age on admission, yr.	57.5
Average age at death, yr.	61.6
Average duration of hospitalization, yr.	4.1

Convulsive seizures occurred in five (7%) cases. One of these patients had had idiopathic epilepsy since childhood; two had post-traumatic encephalopathy, and one had cerebral arteriosclerosis with mutiple cortical infarcts.

Family histories were uniformly noncontributory for the entire group.

The onset of the patients' mental symptoms could not be determined accurately, for they developed in most instances rather insidiously and became progressively worse up to the time of hospital commitment. The average age upon admission was 57.5 years (range, 36 to 88 years), which represents, therefore, the approximate age at which mental symptoms became severe. The average age at death was 61.6 years, so that the average duration of hospitalization was 4.1 years. No improvement in the mental status occurred in any of the cases from the time of admission until death.

On neurologic examination (Table 2), 10 cases (14%) showed evidence of ocular disturbances, 8 of them with inequality and irregularity of pupils and 2 of them with gross ophthalmoplegia. The occurrence of nystagmus was recorded in only one case. Ataxia and incoordination were difficult to evaluate because of the presence of peripheral neuritis in many cases, but they were noted in 24 patients (34%). Gross evidence of peripheral neuritis was recorded in 35 cases (50%).

Seven cases (10%) showed a combination of signs consisting of mental deterioration, ocular disturbances, incoordination, and peripheral neuritis. Neurologic signs of either ocular abnormalities or cerebellar dysfunction were found in 15 cases (21.4%).

One patient had a positive blood Wassermann reaction, but his spinal fluid was negative and he had no clinical stigmata of syphilis.

Examination of the spinal fluid was performed on five other cases and was negative in each of them.

Pathologic Features.—General autopsy revealed a variety of disorders, most of which were cardiovascular or other conditions to be expected in this age group. Pulmonary tuberculosis, which was active in 2 cases, was found in 12 (17%), carcinoma in 12 (17%), and cirrhosis of the liver in 24 (34%).

Gross Examination of the Brain: Abnormally small mammillary bodies with yellowish brown discoloration (Fig. 1*A*) were present in 57 cases (81%). Generalized ventricular dilatation was found in four cases (5.7%).

Histologic Examination (Table 3): The thalamic and hypothalamic periventricular areas showed diffuse gliosis (Fig. 1*B*) in

TABLE 2.—*Neurologic Signs in Seventy Cases of Korsakoff's Syndrome*

Signs	Incidence
Ocular disturbances (pupillary & ophthalmoplegias)	10 (14%)
Ataxia and incoordination	24 (34%)
With cerebellar atrophy on necropsy	12 (17%)
Peripheral neuritis (gross)	35 (50%)
Findings suggestive of chronic Wernicke's syndrome	22 (31.4%)
Complete (mental, neuritis, ocular, *and* cerebellar)	7 (10%)
Incomplete (mental & neuritis, plus ocular *or* cerebellar)	15 (21.4%)
No signs other than mental and neuritis	48 (68.6%)

TABLE 3.—*Neuropathology of Seventy Cases of Korsakoff's Syndrome*

Region	Incidence
Periventricular & periaqueductal region	70 (100%)
Mammillary body	67 (95.7%)
Thalamus (dorsomedial nuclei)	37 (52.8%)
Plus pulvinar	3 (4.2%)
Brain stem nuclei	16 (22.8%)
Quadrigeminal bodies	4 (5.7%)
Oculomotor nuclei	2 (2.8%)
Inferior olives	5 (7.1%)
Vestibular nuclei	5 (7.1%)
Dorsal efferent nuclei of vagus	4 (5.7%)
Cerebellum	24 (34.2%)
Plus dentate nuclei	4 (5.7%)
Cerebral cortex	
"Alzheimer glial change"	9 (12.8%)
"Central neuritis"	6 (8.5%)
Cornu ammonis sclerosis	10 (14.2%)

all 70 cases, with additional granular ependymitis in 2.

The mammillary bodies showed atrophy and gliosis (Fig. 2*A*) in 67 cases (95.7%). In a few the changes were of a subacute nature, with proliferation in the degenerated parenchyma of microglia and gitter cells, while in the majority the reaction consisted of a more chronic response by astrocytes and glial fibers (Figs. 2*B* and 3*A*). Frequently there were proliferative changes in the endothelium of blood vessels and increase in reticulin fibers (Fig. 3*B*), but hemorrhages were extremely rare. On occasion there was focal necrosis associated with marked dropping out of neurons. In most cases, however, there was relative preservation of the neurons, although they had undergone either shrinkage and hyperchromatosis or ischemic changes.

The thalamus showed predominant involvement of its medial parts. The dorsomedial nuclei were involved in 37 cases (52.8%) and the pulvinar in 3 cases (4.2%). The changes differed from those of the mammillary bodies in that the neurons had virtually disappeared (Fig. 4, upper) and were replaced by dense gliosis (Fig. 4, lower), made up of small fibrillary astrocytes and glial fibers.

The brain stem showed periaqueductal gliosis (Fig. 5*A*) in the majority of cases and nuclear pathology in 16 (22.8%), with changes similar to those of the thalamus. These changes occurred in the quadrigeminal bodies in four cases (5.7%), in the oculomotor nuclei (Fig. 5*B*) in two (2.8%), in the inferior olives in five (7.1%, in the vestibular nuclei (Fig. 6, upper) in five (7.1%), and in the dorsal efferent nuclei of the vagus in four (5.7%).

In the cerebellum, there were degenerative changes in 24 cases (34.2%) characterized by diffuse dropping out of Purkinje cells, increase in glial cells of the Bergmann layer, and gliosis of the white matter (Fig. 6,

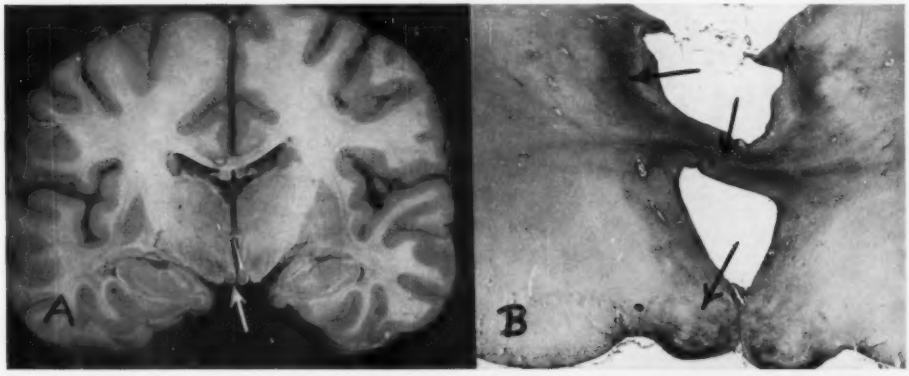


Fig. 1.—*A*, coronal section showing symmetrical atrophy of the mammillary bodies. *B*, gliosis in the walls of the third ventricle, the dorsomedial nucleus of the thalamus, the massa intermedia, and the mammillary bodies. Holzer stain; reduced to 89% of mag. ×3.

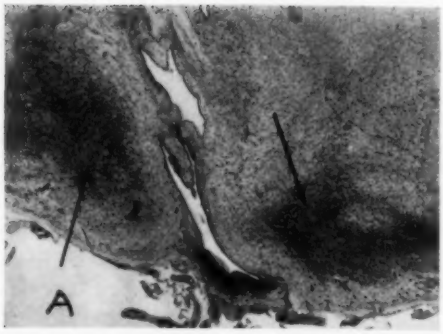
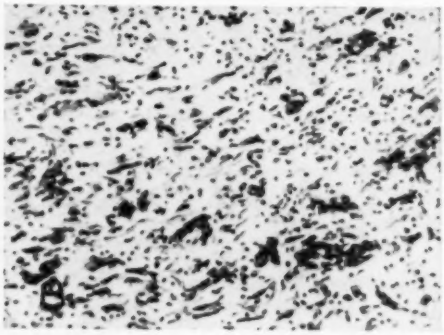


Fig. 2.—*A*, mammillary bodies showing loss of neurons and proliferation of the glia. Nissl stain; reduced to 73% of mag. × 32.



B, proliferation of microglia, astrocytes, and blood vessels, replacing degenerated parenchyma of mammillary bodies. Nissl stain; reduced to 73% of mag. × 250.

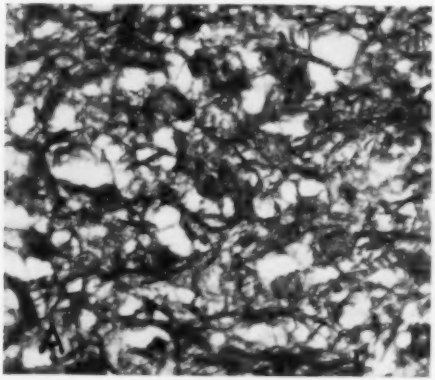
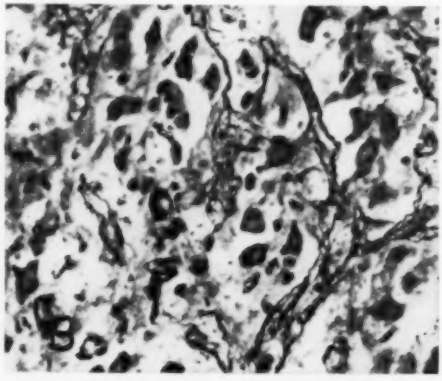


Fig. 3.—*A*, network of glial fibers and scattered hypertrophied astrocytes in the mammillary body. Holzer stain; reduced to 76% of mag. × 345.



B, proliferation of blood vessels and reticulin fibers in mammillary body; Laidlaw stain; reduced to 76% of mag. × 345.

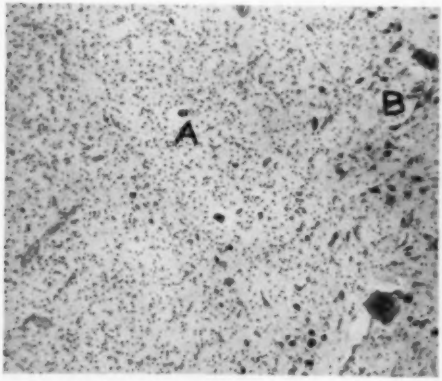
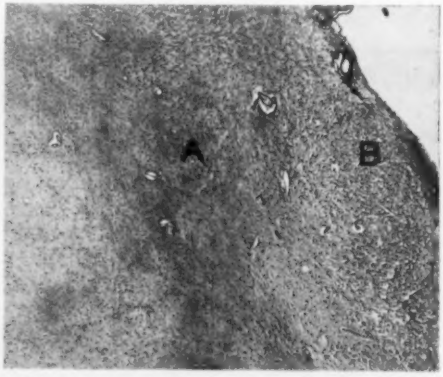


Fig. 4.—Left: Disappearance of the majority of neurons in the dorsomedial nuclei of the thalamus (*A*), contrasting with preservation of periventricular nuclei (*B*). Nissl stain; reduced to 73% of mag. × 65.



Right: Dense gliosis in the dorsomedial nucleus (*A*) and intact periventricular nuclei (*B*) of the thalamus. Holzer stain; reduced to 73% of mag. × 28.

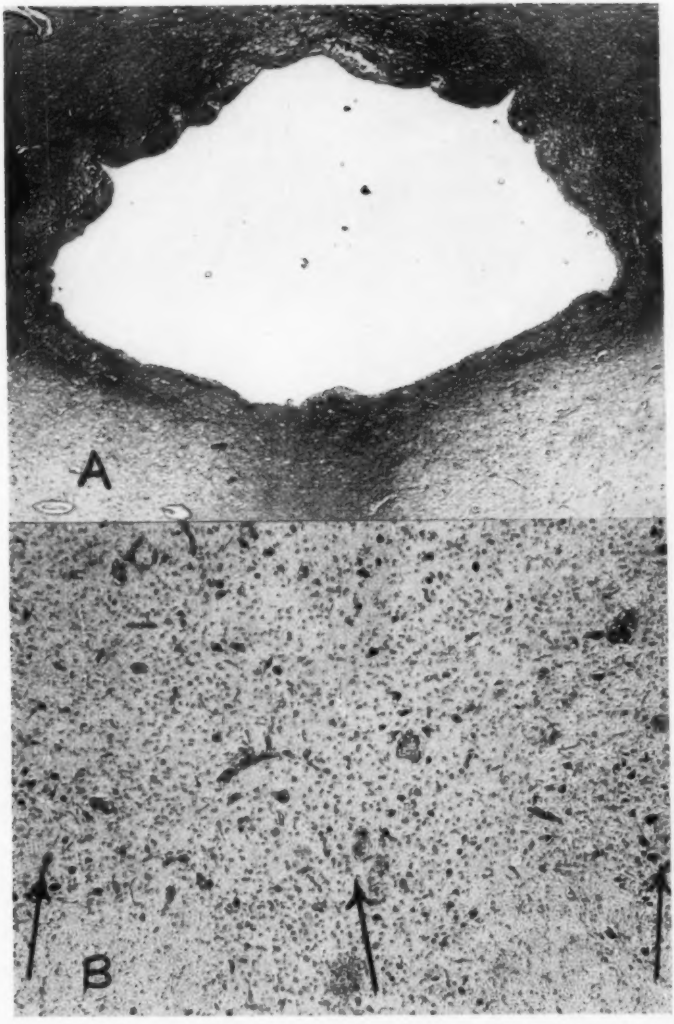


Fig. 5.—*A*, increase in periaqueductal gliosis. Holzer stain; reduced to 92% of mag. ×33.
B, degeneration in the oculomotor nuclei, particularly the medial group. Nissl stain; reduced to 85% of mag. ×38.

lower left). These abnormalities were most prominent in the vermis. Four cases also showed degenerative changes in the dentate nuclei.

The cerebral cortex showed no specific abnormalities. Nine cases (12.8%) revealed diffuse proliferation of abnormally large nuclei, known as Alzheimer glia, accompanied by mild toxic changes in the neurons and occasional increase in microglial elements. These changes commonly occur with liver disease, which was present in each of the cases. Six cases (8.5%) had acute, widespread neuronal changes, characterized by swelling, central chromatolysis, dislocation of the nucleus to the periphery, and concentration of the Nissl bodies at the periphery of the neurons. These changes are often referred to as "central neuritis" (Meyer [3]) and are characteristic findings in cases of pellagra. Cornu ammonis sclerosis was present in 10 cases (14.2%) and was associated with senile brain disease in 3 cases, with traumatic encephalopathy in

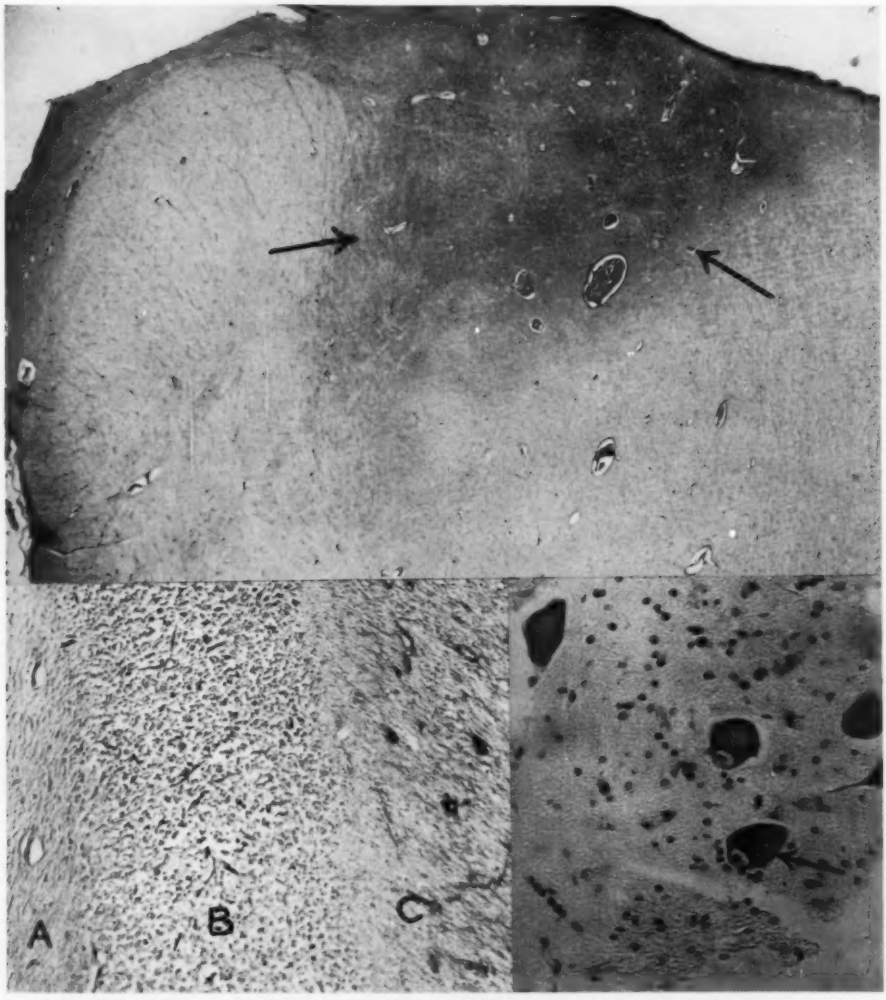


Fig. 6.—Upper: Gliosis in the vestibular region in the floor of the fourth ventricle. Holzer stain; reduced to 89% of mag. ×15.

Lower left: Diffuse degeneration of cerebellum with complete loss of Purkinje layer (*A*), rarefaction of the granular layer (*B*), and gliosis of the white matter (*C*). Holzer stain; reduced to 89% of mag. ×100.

Lower right: Axonal reaction changes of anterior horn cells in association with peripheral neuritis; Nissl stain; reduced to 89% of mag. ×200.

3, with cerebral arteriosclerosis in 2, and with long-standing epilepsy in 2.

The spinal cord was abnormal in 5 of the 12 cases examined, showing paucity of anterior horn cells, the remaining cells demonstrating axonal reaction changes characteristic of peripheral neuritis (Fig. 6, lower right).

Coincidental brain pathology (Table 4) was found in 33 cases (47.1%): senile changes in 10, vascular disease in 10, traumatic contusions in 6, tumor (2 metastatic, 1 neurofibroma, 1 lipoma, and 1 meningioma) in 5, chronic suppurative pachymeningitis associated with skull fracture in 1, and chronic subdural hematoma in 1.

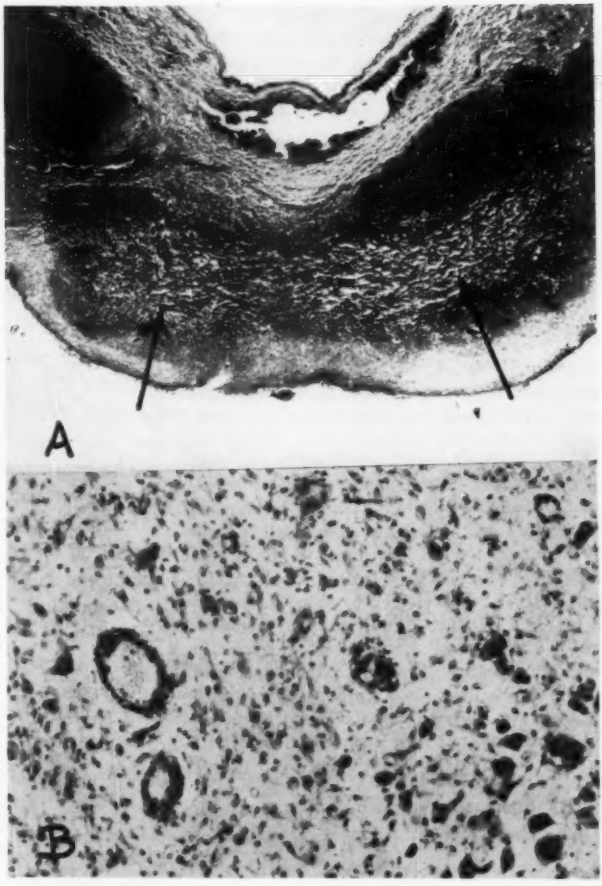


Fig. 7.—*A*, subacute necrosis of mammillary bodies and hemorrhages in the floor of the third ventricle. Hematoxylin-Van Gieson stain; ×15. *B*, vestibular region showing diffuse loss of neurons, axonal reaction in those remaining (lower right field), associated with proliferation of microglia, astrocytes, and perivascular cuffing with lymphocytes. Nissl stain; ×140.

TABLE 4.—*Other Coincidental Brain Pathology in Thirty-Three of the Seventy Cases of Korsakoff's Syndrome*

Brain Pathology	Incidence
Senile changes	10 (14.3%)
Vascular disease	10 (14.3%)
Traumatic contusions	6 (8.6%)
Tumor (2 metastatic, 1 neurofibroma, 1 lipoma, and 1 meningioma)	5 (7.1%)
Chronic suppurative pachymeningitis	1 (1.4%)
Chronic subdural hematoma	1 (1.4%)
General Autopsy Findings	
Pulmonary tuberculosis (active in 2 cases)	12 (17%)
Carcinoma	12 (17%)
Cirrhosis of liver	24 (34%)

Comment

None of the cases in this series showed the acute hemorrhagic brain pathology of Wernicke's encephalopathy but revealed subacute or chronic degenerative changes. These might be interpreted either as residual effects of previous acute Wernicke's disease or as chronic, slowly progressive degeneration. The former possibility was suggested in the two following cases.

CASE 1.—A 60-year-old alcoholic housewife had a relatively rapid onset of confusion and irrational behavior and was stuporous on admission. Examination revealed that she had intermittent, spasmodic generalized tremors; marked memory impairment; disorientation; irrelevant and inco-

herent speech; slow, labored thinking, and confabulation. She talked to herself and heard voices. There were signs of severe polyneuritis, asthenia, and incoordination. Her condition remained unchanged until her death, six months after the onset of symptoms. Pathologically, the mammillary bodies revealed focal areas of necrosis, with large numbers of gitter cells and occasional hemorrhages which replaced the parenchyma (Fig. 7*A*), indicating a relatively subacute disorder. In the thalamus, however, the reaction was purely astrocytic. Clinically, the patient presented a mixed picture of Wernicke's disease and Korsakoff's syndrome.

Case 2.—A distinct history of a previous attack of Wernicke's encephalopathy was obtained in a patient who, at the age of 56, developed rather abruptly a severe illness characterized by stupor, disorientation, memory impairment, confusion, irregular and unequal pupils, nystagmus, dysarthria, incoordination, malnourishment, and peripheral neuritis. His condition slowly improved, and in several years he was up and about, without any particular neurologic defects other than a constant head tremor. However, the picture of Korsakoff's syndrome, with loss of memory, disorientation, and confabulation, persisted unchanged until his death, at age 70. Microscopic examination of the brain showed focal areas of gliosis in subependymal zones of the aqueduct and third and fourth ventricles, and chronic degenerative changes in the mammillary bodies, the medial nuclei of the thalamus, the oculomotor and vestibular nuclei, the inferior olives, and the superior vermis of the cerebellum.

This case illustrates the frequent observation that patients who survive an attack of "acute hemorrhagic polioencephalitis superior" often show improvement of or complete recovery from the ocular disturbances and ataxia, but many of them are left with a residual Korsakoff psychosis (Cruickshank [4], Jolliffe, Wortis, and Fein [5], Victor, Hope, and Adams [6]).

A relatively acute clinical course occurred in only one case of this series.

Case 3.—A 55-year-old chronic alcoholic exhibited memory impairment, disorientation, and confusion for one month before abruptly becoming completely irrational, bedridden, and, finally, moribund, over a three-day period, ending in death. Neuropathologic study revealed proliferating microglia, hypertrophic astrocytes, and inflammatory changes in the mammillary bodies, medial nuclei of the thalamus, medial oculomotor nuclei, dorsal efferent nuclei of the vagus, and vestibular nuclei (Fig. 7*B*). These acute changes were superimposed upon a more chronic gliosis. It is reasonable to assume that the chronic changes accounted for the symptoms of Korsakoff's psychosis, while the superimposed acute changes were responsible for his terminal illness, which was suggestive of Wernicke's disease.

These three cases thus presented combinations of the two syndromes. The first patient had a relatively acute onset of both syndromes, which persisted until her death, in six months; the second patient recovered from an acute attack of Wernicke's encephalopathy but was left with residual Korsakoff's psychosis until his death, 14 years later, while the third patient developed at first a Korsakoff psychosis of one month's duration, followed by acute Wernicke's disease just prior to his death.

The brain pathology in the remaining 67 cases represented chronic degenerative disorders. This corresponded to an insidious onset and chronic progression of signs and symptoms in all of them.

Although all 70 cases manifested the clinical picture of Korsakoff's psychosis, 7 (10%) showed, in addition, chronic neurologic signs of a complete and 15 (21.4%) of a partial Wernicke syndrome. Thus, 22 cases (31.4%) exhibited neurologic signs and 48 cases (68.6%) no abnormal neurologic signs other than peripheral neuritis. It is likely, however, that adequate neurologic examinations were not performed, and only gross signs of central nervous system disturbances were reported. For example, clinical evidence of cerebellar dysfunction was not recorded in one-half of the 24 cases that showed cerebellar degeneration histologically. Likewise, peripheral neuritis, which was noted in 50%, presumably occurred more frequently in less severe form but was overlooked.

The clinical association of the two syndromes has been frequently cited in the literature (Bender and Schilder [7]; Campbell and Biggart [8]; Campbell and Russell [9]). Victor, Hope, and Adams [6] found that 73% of 59 chronic alcoholics with Wernicke's disease had an associated Korsakoff's psychosis. All reports, however, have considered the two conditions as separate disease entities.

The present study shows that they may occur simultaneously in acute or chronic form, either as complete or as incomplete syndromes. The implication is clear that each syndrome represents merely a different clinical expression of the same disorder. The particular clinical syndrome appears to be dependent only upon the tempo, severity, and extent of the underlying disease process.

Relatively few comprehensive pathologic studies have been reported on the two syndromes.

The brain changes associated with Wernicke's disease were described in 21 cases by Campbell and Russell,[9] though the histologic study was incomplete in many of them. Riggs and Boles [10] reported on 42 cases, of which 13 were not thoroughly investigated. A study by de Wardener and Lennox [11] was concerned primarily with the clinical evaluation of 52 cases; out of 21 deaths, 16 brains were available for investigation and only gross examinations were made, 8 showing hemorrhages in the mammillary bodies. These reports, as well as a number of others of less magnitude, have been concerned primarily with the hemorrhagic changes in the brain occurring in acute Wernicke's encephalopathy. Many of the lesions described in individual cases, however, were those of a "subacute," "chronic," or "healed" nature (Campbell and Biggart [8]; Boles and Boles Jr.[12]; Neubürger [14]; Meyer [18]).

A detailed report of 16 cases by Gamper [15] (1928) represents the only previous comprehensive pathologic study of Korsakoff's psychosis. The course of the illness in the majority of cases was acute, with a duration of 8 to 14 days. The exact nature of the clinical picture in his cases is unknown, for he failed to elaborate on the findings beyond the fact that they showed Korsakoff's mental picture "with or without the narrower clinical syndrome of polioencephalitis hemorrhagica superior," and he did not attempt to differentiate the two conditions in his pathologic discussion. He apparently used the terms Wernicke and Korsakoff interchangeably and did not express an opinion as to the possible relationship of the two syndromes.

The distribution of lesions in the present study (Table 3) closely coincides with that in Gamper's cases. Localization was predominant in the periventricular gray matter, in the mammillary bodies, and in the medial regions of the thalamus, especially the dorsomedial nuclei, while the cerebellum and selected areas in the brain stem were less frequently affected.

One of the consistent histopathologic features of our cases was the intense gliosis in the involved areas. In the mammillary bodies it was associated with relative preservation of neurons, indicating a primary irritation of the glia. However, in the dorsomedial nuclei of the thalamus there was a direct correlation between the disappearance of neurons and the glial replacement. "Vascular proliferation" was inconstant, and when it occurred it was confined almost entirely to the mammillary bodies. According to Alexander,[16] angionecrosis is a primary factor in the clinical and experimental Wernicke lesion. From our study, it would appear that the primary site of the lesion varies and may be parenchymal, glial, or vascular. Hemorrhage was rarely observed in our cases, and that is in agreement with the findings of Gamper.

Cerebellar degeneration has been frequently observed in cases of chronic alcoholism (Lhermitte[17]; Romano, Michael, and Merritt [18]; Sántha [19]; Skillicorn [20]). In this study 2 of the 7 nonalcoholic and 22 of the 63 alcoholic patients revealed cerebellar pathology. Only 12 of the 70 cases showed both clinical and pathologic evidence of cerebellar disease. Another 12 cases had ataxia on clinical examination but no necropsy findings of cerebellar abnormality; the incoordination in these may have been due to impairment of position sense resulting from peripheral neuropathy.

The pathogenesis of the mental symptoms is not well understood. Carmichael and Stern [21] felt that the cortical changes of

"central neuritis," which have been described in pellagra (Singer and Pollock [22]), may have been responsible for the Korsakoff psychosis in their five cases. Gamper attributed the mental abnormalities to lesions in the mammillary bodies, particularly since in some cases the pathology was restricted to this area. Delay and Brion [23] thought that degeneration of mammillary bodies accounted for the psychosis in their single case. Nielson [24] concluded that the mental picture in acute Wernicke's disease resulted from the interruption of projection fibers from the hypothalamus and thalamus to the frontal lobes and to the anterior cingulate gyri.

In this study there was no correlation between the Korsakoff psychosis and cortical pathology. Only 8.5% of the cases revealed diffuse cortical changes in the form of "central neuritis," while the remainder showed no cortical lesions. On the other hand, 100% showed hypothalamic-thalamic periventricular pathology. In four cases with generalized ventricular dilatation there was no cortical atrophy, and the periventricular gliosis was sufficiently severe to have accounted for the ventricular enlargement.

The implication that mental disturbances may result from hypothalamic and thalamic, rather than from cortical, pathology is not new (Hess [25]; MacLean [26]; Papez [27]). Though intellectual functions are carried on in the neopallium, affective behavior appears to be dominated by a relatively crude and phylogenetically old system, composed of the hippocampal formation with the fornix, hypothalamus, anterior thalamic nuclei, and cingulate gyrus, and their connections. The experiments of Bard [28] have demonstrated that emotional expression depends on the integrating action of the hypothalamus. It is hardly a coincidence that in the present study every one of the 70 cases with involvement either of the mammillary bodies (95.7%) or of the dorsomedial nuclei of the thalamus (52.8%) showed similar mental aberrations. In 33 cases (41.7%) other, unrelated brain pathology, such as senile and arteriosclerotic changes, conceivably could have been a contributing factor in the production of the abnormal mental picture. These abnormalities, however, were undoubtedly superimposed upon the primary disease, for in practically every instance such pathology was shown from clinical investigation to have occurred some time after the appearance of the Korsakoff syndrome.

The etiology of the Wernicke and Korsakoff syndromes is unknown, though there is available considerable evidence which would seem to implicate dietary deficiencies, specifically that of thiamine. Animal experiments have shown that lesions similar to those found in acute hemorrhagic polioencephalitis superior are consistently produced by thiamine-deficient diets, but not with other deficiencies (Alexander [16]; Zimmerman [29]). Although both syndromes occur predominantly in alcoholic patients, they are not uncommon in nonalcoholics, in whom malnourishment is a constant feature (Wernicke [1]; Korsakoff [2]). This was also borne out in our series. It is logical to assume that dietary discrepancies exist in many, but not in all, alcoholic patients. It is also possible that alcohol interferes with the absorption or proper utilization of thiamine, perhaps as a result of impaired gastrointestinal or liver function. Wortis, Bueding, Stein, and Jolliffe [30] found that patients with Wernicke's disease invariably show an elevation of blood pyruvate, which rapidly returns to normal after thiamine administration, and they concluded that patients with this syndrome fail to metabolize properly pyruvic acid, a product of carbohydrate metabolism. There are many well-documented reports of dramatic improvement occurring in cases of Wernicke's encephalopathy following thiamine therapy (Cruickshank [4]; Jolliffe, Wortis, and Fein [5]; Victor, Hope, and Adams [6]; de Wardener and Lennox [11]; Boles and Boles Jr.[12]). Korsakoff's psychosis, however, responds poorly to vitamin therapy.

Conclusions

It is evident from this study that the consistent brain pathology of Korsakoff's psychosis is characterized primarily by degenerative changes in the periventricular and periaqueductal gray matter, the mammillary bodies, and the dorsomedial nuclei of the thalamus, and less frequently in the brain stem and cerebellum. The distribution of the lesions is identical with that of Wernicke's syndrome. There is no evidence of specific cortical pathology in this condition. The findings indicate that the Wernicke and Korsakoff syndromes are identical disorders, probably resulting directly or indirectly from thiamine deficiency. The two syndromes merely depend on the acuteness or chronicity, respectively, of the underlying disease process. Previous investigations indicate that early and adequate treatment with thiamine hydrochloride frequently may bring about a remission of symptoms of the acute Wernicke syndrome but rarely improves the Korsakoff psychosis. The invariable involvement of the periventricular hypothalamic and thalamic regions in these cases, and particularly the mammillary bodies, demands strong consideration in regard to pathogenesis of the mental symptoms, especially since they cannot be attributed to cortical pathology.

Summary

A comprehensive clinicopathologic study has been made of 70 cases with Korsakoff's syndrome, 90% of whom were alcoholics.

The specific nature of the neuropathology is established, and the relationship of the Wernicke and the Korsakoff syndrome is discussed.

REFERENCES

1. Wernicke, C.: Lehrbuch der Gehirnkrankheiten, Berlin, 1881, Vol. 2, pp. 229-242.

2. Victor, M., and Yakovlev, P. I.: S. S. Korsakoff's Psychic Disorder in Conjunction with Peripheral Neuritis: A Translation of Korsakoff's Original Article with Brief Comments on the Author and His Contribution to Clinical Medicine, Neurology 5:394, 1955.

3. Meyer, A.: On Parenchymatous Systemic Degenerations Mainly in the Central Nervous System, Brain 24:47, 1901.

4. Cruickshank, E. K.: Wernicke's Encephalopathy, Quart. J. Med. 19:327, 1950.

5. Jolliffe, N.; Wortis, H., and Fein, H. D.: The Wernicke Syndrome, Arch. Neurol. & Psychiat. 46:569, 1941.

6. Victor, M.; Hope, J. M., and Adams, R. D.: A Clinical Study of Wernicke's Disease, Tr. Am. Neurol. A. 77:178, 1952.

7. Bender, L., and Schilder, P.: Encephalopathia Alcoholica; Polioencephalitis Haemorrhagica Superior of Wernicke, Arch. Neurol. & Psychiat. 29:990, 1933.

8. Campbell, A. C. P., and Biggart, J. H.: Wernicke's Encephalopathy (Polioencephalitis Hæmorrhagica Superior): Its Alcoholic and Non-Alcoholic Incidence, J. Path. & Bact. 48:245, 1939.

9. Campbell, A. C. P., and Russell, W. R.: Wernicke's Encephalopathy: The Clinical Features and Their Probable Relationship to Vitamin B Deficiency, Quart. J. Med. 10:41, 1941.

10. Riggs, H. E., and Boles, R. S.: Wernicke's Disease: A Clinical and Pathological Study of 42 Cases, Quart. J. Stud. Alcohol 5:361, 1944.

11. de Wardener, H. E., and Lennox, B.: Cerebral Beri-Beri (Wernicke's Encephalopathy): Review of 52 Cases in Singapore Prisoner-of-War Hospital, Lancet 1:11, 1947.

12. Boles, R. S., and Boles, R. S., Jr.: Wernicke's Disease: Clinical and Pathological Study of 9 Cases, Gastroenterology 19:504, 1951.

13. Meyer, A.: The Wernicke Syndrome, with Special Reference to Manic Syndromes Associated with Hypothalamic Lesions, J. Neurol. Neurosurg. & Psychiat. 7:66, 1944.

14. Neubürger, K.: Wernickesche Krankheit bei chronischer Gastritis: Ein Beitrag zu den Beziehungen zwischen Magen und Gehirn, Ztschr. ges. Neurol. u. Psychiat. 160:208, 1937.

15. Gamper, E.: Zur Frage der Polioencephalitis hæmorrhagica der chronischen Alkoholiker: Anatomische Befund beim alkoholischen Korsakow und ihre Beziehungen zum klinischen Bild, Deutsche Ztschr. Nervenh. 102:122, 1928.

16. Alexander, L.: Wernicke's Disease: Identity of Lesions Produced Experimentally by B_1 Avitaminosis in Pigeons with Hemorrhagic Polioencephalitis Occurring in Chronic Alcoholism in Man, Am. J. Path. 16:61, 1940.

17. Lhermitte, J.: Cortical Cerebellar Degeneration, Proc. Roy. Soc. Med. 28:379, 1935.

18. Romano, J.; Michael, M., and Merritt, H. H.: Alcoholic Cerebellar Degeneration, Arch. Neurol. & Psychiat. 44:1230, 1940.

19. Sántha, K.: Lokalisierte Atrophie der Kleinhirnrinde bei chronischem Alkoholismus, Monatsschr. Psychiat. u. Neurol. 116:346, 1948.

20. Skillicorn, S. A.: Presenile Cerebellar Ataxia in Chronic Alcoholics, Neurology 5:527, 1955.

21. Carmichael, E. A., and Stern, R. O.: Korsakoff's Syndrome: Its Histopathology, Brain 54: 189, 1931.

22. Singer, H. D., and Pollock, L. J.: The Histopathology of the Nervous System in Pellagra, Arch. Int. Med. 11:565, 1913.

23. Delay, J., and Brion, S.: Syndrome de Korsakoff et corps mamillaires, Encéphale 43:193, 1954.

24. Nielson, J. M.: Wernicke's Encephalopathy: Correlation of Sites of Lesions with Symptomatology, J. Nerv. & Ment. Dis. 118:429, 1953.

25. Hess, W. R., and Akert, K.: Experimental Data on Role of Hypothalamus in Mechanism of Emotional Behavior, A. M. A. Arch. Neurol. & Psychiat. 73:127, 1955.

26. MacLean, P. D.: The Limbic System ("Visceral Brain") and Emotional Behavior, A. M. A. Arch. Neurol. & Psychiat. 73:130, 1955.

27. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. 38:725, 1937.

28. Bard, P.: A Diencephalic Mechanism for the Expression of Rage, with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. 84:490, 1928.

29. Zimmerman, H. M.: The Pathology of the Nervous System in Vitamin Deficiencies, Yale J. Biol. & Med. 12:23, 1939.

30. Wortis, H.; Bueding, E.; Stein, M. H., and Jolliffe, N.: Pyruvic Acid Studies in the Wernicke Syndrome, Arch. Neurol. & Psychiat. 47:215, 1942.

Early Ambulation and Psychotherapy for Treatment of Closed Head Injury

RAGNAR MÜLLER, M.D.
and
BENGT NAUMANN, M.D., Stockholm

Investigations during and immediately after the Second World War revealed that the pretraumatic personality, the emotional reaction to the accident, and environmental factors are of great importance in the development of persistent symptoms subsequent to closed head injuries (the postconcussion syndrome).* This observation influenced the traditional concept that prolonged rest in bed is essential after an acute head injury. Early physical activity was instituted by some workers,† and psychotherapy was recommended ‡ but was apparently never tested systematically.

The present study concerns a series of 258 closed head injuries treated with early ambulation and psychotherapy. A report is given of the immediate results and of a follow-up. The principles of the treatment and the causes of the postconcussion syndrome are discussed.

Material

The series consists of consecutive cases admitted to Serafimerlasarettet from February, 1953, to February, 1955, for treatment of acute head injuries. To facilitate the follow-up, we included only patients resident in or near Stockholm. The patients ranged in age from 13 to 79. The original material consisted of 277 patients. Fourteen died in the hospital. Four were eliminated from the outset; two of them suffered from advanced senile dementia; one was a young girl with active schizophrenia, and one was an older man who became mentally confused soon after admission and was referred to a mental hospital. A fifth patient broke off treatment. Otherwise the material was not selected.

Sex and Age.—The age and sex distribution of the patients is shown in Table 1. As is usual in accident cases, men were in the majority. Almost half the patients were 40 years of age or older.

Occupation.—The occupational distribution is given in Table 2. Most of the patients were manual workers, but 26% were students, professionals, or office workers.

Pretraumatic Mental State.—No intelligence tests were conducted, but the I. Q. of the five patients listed in Table 3 as mentally defective was obviously low. Mild neurotic disturbances were considered to be present in patients who for a long period before the accident, often since childhood, had been nervous, restless, and anxious, and who had reacted to reverses with depression, anxiety, insomnia, etc. They were well adjusted socially and usually had a good working capacity.

Psychologic Stress.—Every fifth patient reported psychologic stress at the time of the accident (Table 4). The commonest causes were domestic or occupational conflicts.

Post-Traumatic Amnesia.—The duration of the post-traumatic amnesia (PTA) was recorded when the patient was discharged, at which time the amnesia had reached a stable minimum (Table 5). Twenty-three patients (9%) had no amnesia. In 43% of the cases post-traumatic amnesia lasted one hour or more. Amnesia in excess of 24 hours was found in 10% of the patients.

Fracture of Skull.—Practically all the patients were examined roentgenographically. Fracture of the convexity and/or the base of the skull was seen in 23% (Table 6).

Neurologic Signs.—The signs observed in the period immediately following the injury are listed in Table 7. Abnormalities in reflex responses are not included. Many more than the five patients mentioned in Table 7 had blood-stained spinal fluid. However, these five had massive subarachnoid hemorrhage with sigus of meningeal irritation, including fever, nuchal stiffness, and Kernig's sign.

Received for publication May 9, 1956.

From the Neurologic Clinic of Serafimerlasarettet.

* References 1-9.

† References 2, 3, 10, 11.

‡ References 1, 6, 8, 9, 12, 13.

TABLE 1.—*Age and Sex Distribution*

Sex	Age, Years							Total
	13-19	20-29	30-39	40-49	50-59	60-69	70-79	
Men	26	42	42	41	30	14	15	210
Women	10	10	6	6	9	5	2	48
Total	36	52	48	47	39	19	17	258

TABLE 2.—*Occupational Distribution*

	Total
Manual workers	111
Service personnel	40
Office workers	40
Professionals and students	26
Housewives	9
Self-employed	19
Pensioners	13
Total	258

TABLE 3.—*Pretraumatic Mental State*

	No. of Cases
No demonstrable mental abnormality	143
Mentally defective	5
Psychopathic personality	15
Alcoholism	28
Pronounced neurotic disturbances	17
Mild neurotic disturbances	50
Total	258

TABLE 4.—*Psychologic Stress at Time of Accident*

	No. of Cases
No stress situation	206
Domestic conflict	15
Occupational conflict	11
Conflict with parents	4
Unemployment	7
Lack of living quarters	7
Illness or death in family	5
Other	3
Total	258

As might be expected, the frequency of neurologic signs increased with the duration of post-traumatic amnesia. The most serious conditions were observed in patients with PTA of more than 24 hours. Neurosurgery was performed in 18 patients.

Methods

The patients were kept in bed for the first 24 hours after the accident. However, they were permitted to move freely in bed, sit up, read, listen to the radio, receive visitors, etc. Those who were willing and able were also allowed to get up to visit the bathroom. Unconditional rest in bed thus was not prescribed except in the case of massive subarachnoid hemorrhage and after surgery.

TABLE 5.—*Duration of Post-Traumatic Amnesia*

No. of Cases	Time								Total
	0	<1 Min.	1-10 Min.	11-59 Min.	1-5 Hr.	6-24 Hr.	1-7 Days	7 Days—	
Absolute	23	18	46	60	62	22	16	11	258
Percentage	9	7	18	23	24	9	6	4	100

TABLE 6.—*Fractures of Skull*

	Bones of Face	Convexity	Base	Convexity + Base	No Fracture	Total
No. of cases	27	25	8	26	172	258

TABLE 7.—*Neurologic Signs*

Signs	Duration of Post-Traumatic Amnesia, Hours			Total
	<1	1-24	>24	
Anosmia		6	2	8
Unilateral optic atrophy with blindness			1	1
Cortical blindness			1	1
Diplopia	1	4	2	7
Trigeminal nerve injury	4	2		6
Unilateral facial paralysis		2	4	6
Unilateral deafness	2	5	1	8
Nystagmus with or without vertigo	11	5	3	19
Hemiparesis			4	4
Aphasia		1	1	2
Epileptic seizures		2	3	5
Subarachnoid hemorrhage		1	4	5
Total	18	28	26	72

As the patients became lucid and free from headache and dizziness, they were allowed to dress and move around the ward. Some of the patients were up and about even with headache and dizziness. A few experienced nausea and dizziness or vertigo when they tried to get up, but this was not considered a reason for further rest in bed for any length of time. Instead, the patients were urged to try to get up later in the day or on the next day in order to become quickly accustomed to being ambulatory. Nervousness, anxiety, restlessness, poor memory, sleeping difficulties, etc., were not indications for confinement to bed. On the contrary, physical activation was instituted especially early in cases of these disturbances.

Table 8 shows the length of the stay in bed in relation to PTA. Eighteen patients are not included in this Table. These had incurred severe extracranial injuries in the accident, which required a considerably longer stay in bed than the head injury. Fifty-three per cent of the patients became ambulatory on the second to the fourth day after the accident. Only 28 (12%) were bedfast for more than one week. Five of these had massive subarachnoid hemorrhages, and eight of them had undergone neurosurgery. Five other patients found it difficult to be up for the first week, owing to extensive facial injuries. The majority of the 28 patients had protracted PTA, 19 of them longer than two days. It was among these patients that the severest neurologic disorders were observed. Two patients were kept in bed for over a week for psychotherapeutic reasons.

The difference in duration of rest in bed with PTA of less than one hour and with PTA of 1 to 24 hours was so slight that it can be explained by chance variations. The severity of headache or dizziness was not related to the duration of amnesia.

Verbal psychotherapy was instituted as soon as the patients were lucid. It could usually be confined to soothing reassurances that nothing serious had happened, that any symptoms usually disappear quickly and need not indicate injury to the brain,

TABLE 8.—*Duration of Confinement to Bed According to Duration of Post-Traumatic Amnesia*

Confinement to Bed, Days	Post-Traumatic Amnesia, Hr.			Total No. of Cases	
	<1	1-24	>24	Absolute	Percentage
1-3	80	37	1	127	53
4-7	48	33	4	85	35
8-14	2	6	11	19	8
15-	--	1	8	9	4
Total	139	77	24	240	100

TABLE 9.—*Length of Hospitalization According to Duration of Post-Traumatic Amnesia*

Hospitalization, Days	Post-Traumatic Amnesia, Hr.			Total No. of Cases	
	<1	1-24	>24	Absolute	Percentage
3-7	102	40	4	146	62
8-14	34	25	2	61	26
15-21	1	10	8	19	8
22-28	--	2	4	6	3
29-	--	--	4	4	1
Total	137	77	22	236	100

etc. In other words, it represented supportive therapy in the form of guidance, reassurance, persuasion, and suggestion. In 44 cases (17%) short-term psychoanalytically oriented therapy was carried out. Most of these patients had shown signs of nervousness and restlessness during the first days in the hospital, and their headache and dizziness did not run the "usual" course. Some of them were put under treatment upon the appearance of a postconcussion syndrome after a short symptom-free period.

As a rule the patients were ambulatory in the ward for a few days before discharge. One condition for discharge from the hospital was that the patient had been up for an entire day without serious discomfort. The length of hospitalization in relation to PTA is shown in Table 9. Twenty-two patients are eliminated because their hospitalization was materially extended, due to extracranial injuries. Eighty-eight per cent of the patients left the hospital within two weeks. The 29 patients hospitalized for more than two weeks include the 28 mentioned above, who were bedfast for more than one week.

Patients with PTA of 1 to 24 hours were hospitalized longer than those with shorter PTA. The difference is statistically significant and can be explained, at least in part, by the fact that the former patients had more cranial nerve disorders and severer injuries to the face and limbs.

The patients spent a few days to one week at home after discharge from the hospital and then reported for a check-up at the outpatient department. The majority were found to be symptom-

TABLE 10.—*Duration of Disability According to Duration of Post-Traumatic Amnesia*

Duration of Disability, Days	Post-Traumatic Amnesia, Hr.			Total No. of Cases	
	<1	1-24	>24	Absolute	Percentage
8-14	73	29	4	106	45
15-28	51	25	3	79	34
29-42	11	19	2	32	14
43-56	1	1	6	8	3
57-	2	2	5	9	4
Total	138	76	20	234	100

TABLE 11.—*Patients in Whom Disability Was Markedly Prolonged by Extracranial Injuries or by Somatic Disease (Two Patients)*

Duration of Craniocerebral Symptoms, Days	Post-Traumatic Amnesia, Hr.			Total
	<1	1-24	>24	
1-14	7	5	2	14
15-28	2	--	3	5
29-42	1	2	1	4
43-56	--	1	--	1
Total	10	8	6	24

free and were discharged as cured. Those who had headache or mental disturbances returned for psychotherapy two or three times weekly.

Results

The duration of the disability in relation to PTA is shown in Table 10. This Table includes only 234 patients. The remaining 24, whose disability was prolonged by extracranial injuries or by a somatic disease, are presented in Table 11.

The loss of working time was at most four weeks in 79% of the cases. Only nine patients (4%) were disabled for longer than 8 weeks, three of them for 2½ months, one for 3 months, one for 4 months, one for 5 months, one for 6 months, one for 8 months, and one for 10 months. A brief description of these cases follows.

CASE 1.—A girl aged 16 sustained a depressed skull fracture in a traffic accident. She had amnesia for four days. Operation for the fracture was followed by a brief period of hemiparesis. There was no headache, dizziness, or nervous disturbances. The patient was disabled for two and a half months.

CASE 2.—A woman aged 23 was injured in a traffic accident. She was unconscious for one week and had post-traumatic amnesia for one month. The skull and pelvis were fractured. There were right-sided hemiparesis and aphasia. The aphasia and hemiparesis regressed considerably over a period of six months. The pelvic fracture united. The patient then began to work part time. She showed slight mental deterioration but had no headache or dizziness.

CASE 3.—A man aged 39 fell from a height of 10 meters, after which accident he was unconscious for one week and disoriented for six months. The fall caused a depressed fracture of the occipital bone, which, despite immediate operation, led to blindness. For a while after the operation he suffered left-sided Jacksonian attacks. He showed mental deterioration and mild permanent left-sided hemiparesis. There was no headache, dizziness, or nervous disturbances. The condition was considered to be stationary after 10 months, at which time the patient was still totally disabled.

CASE 4.—A woman aged 35 had been attacked and beaten unconscious. Post-traumatic amnesia lasted one week. There was fracture of the right parietal and temporal bones. There was loss of hearing in the right ear, which gave no response to the caloric test. Total right-sided facial paralysis developed. The patient was nervous and anxious for the first few months. Four months after the accident she began to have epileptic attacks. She returned to work five months after the accident, despite the facial paresis and occasional epileptic attacks.

CASE 5.—A man aged 30 was injured in a traffic accident. He was unconscious for 24 hours and disoriented for 11 days. There was fracture of the left temporal bone, which led to facial paresis. The patient had had migraine since childhood. For several years prior to the accident he had had domestic trouble. His wife suffered from a compulsion neurosis. Soon after the accident the patient began to complain of headache, nervousness, and restlessness. These symptoms regressed in one month with psychotherapy. Nevertheless, the patient could not work for three months because, as a head waiter, he was disabled as long as the facial paresis remained.

CASE 6.—A man aged 62 had a fall downstairs and was unconscious for a few minutes. Post-traumatic amnesia lasted three hours. Two years previously the patient, who was a civil servant, considered he had not been given a promotion which he deserved and his appeal for a reversal of the decision had been denied. The day after the accident he assumed he would be pensioned as an invalid. A typical postconcussion syndrome developed. After two and a half months of intensive psychotherapy the patient was discharged as cured and was able to return to full employment.

CASE 7.—A man aged 38 sustained a depressed fracture in the right frontal bone in an explosion. Post-traumatic amnesia lasted a few minutes. The fracture was treated surgically. For about six months before the accident the patient had been in a state of emotional tension in connection with a divorce case resulting from his wife's infidelity, as well as with financial difficulties. After the accident the patient began to have pain at the site of the fracture and increasing nervousness and difficulty in concentrating. He was unable to work for two and a half months and was given psychotherapy. He then returned to his former occupation as a self-employed businessman, but considered that his capacity for work was impaired.

CASE 8.—A man aged 48 incurred a head injury in a traffic accident. Post-traumatic amnesia lasted two hours. The patient was alcoholic and had mild dementia. Just before the accident he had moved with his family to Stockholm but had not been able to find adequate living quarters. At the same time he took on an exacting job. After the accident he complained of headache, dizziness, and nervousness and was placed under psychotherapy. One month after his discharge from the hospital we lost contact with the patient, who went to another physician. He did not return to us until five months later. He was disabled altogether for eight months.

TABLE 12.—*Period Between Final Discharge and Follow-Up*

No. of Patients	No. of Months						Total
	3-5	6-8	9-11	12-14	15-17	18-20	
Absolute	8	11	101	76	39	23	258
Percentage	3	4	39	29	15	9	100

CASE 9.—A woman aged 45 incurred a skull injury in a traffic accident. Post-traumatic amnesia lasted a few minutes. A phobia developed after the accident—when she entered a bus or an automobile, she became extremely anxious and vomited. Otherwise she had no symptoms. The patient lived outside town at a considerable distance from her place of work. She was absent from work for four months.

When the patients were given their final discharge, all but eight were able to return to their former occupations. Jobs were found during convalescence for seven patients who had been unemployed at the time of the accident. Four of the eight exceptions were due to a somatic disease not connected with the accident. Three patients (Cases 2, 3, and 7) were described in the foregoing section. The eighth patient, who incurred a severe head injury, was a locomotive engineer. When he went back to work, he was first given an office job.

Table 11 covers the 24 patients not included in Table 10. The craniocerebral symptoms did not last more than eight weeks in any of these cases.

We visited and examined 248 patients after an average period of 12 months had elapsed since their final discharge (Table 12). Ten patients could not be traced. With very few exceptions we had had no contact with the patients since their final discharge.

None of the patients had been unfit for work since they were discharged as cured or had been compelled to change to a less strenuous occupation because of sequelae of the head injury. Working conditions were the same as before the accident in 237 cases. Eleven patients had changed occupations since the accident, but this change was due to the head injury in only three cases. Two patients (Cases 2 and 7) had been working ever since their final discharge, but their

TABLE 13.—*Working Conditions and Residual Signs and Symptoms at Follow-Up*

No. of Patients	Period Between Final Discharge and Follow-Up, Months					Total
	3-8	9-11	12-14	15-17	18-20	
Unchanged working conditions						
Free from signs and symptoms	16	78	56	27	14	191
Cranial nerve disorders	--	10	6	3	1	20
Personality changes	--	--	4	1	1	6
Epilepsy	--	--	1	--	1	2
Headache, dizziness, anxiety, nervousness, or difficulty in concentrating	1	8	3	4	2	18
Changed working conditions						
Extracranial fracture or somatic disease	2	3	3	--	--	8
Sequelae of head injury	--	--	2 (Cases 2,3)	--	1 (Case 7)	3
No follow-up	--	2	1	4	3	10
Total	19	101	76	39	23	258

working capacity was reduced by approximately 25%. The third patient (Case 3) was completely disabled.

Forty-six patients, who were working full time, had signs or symptoms which could be referred to the head injury (Table 13). Persistent cranial nerve disorders were to blame in 20 cases. Six patients showed slight personality changes without any real symptoms. According to their relatives, however, their personalities were definitely changed. Two other patients had epileptic attacks. Eighteen patients had symptoms in the form of headache, dizziness, anxiety, nervousness, or difficulty in concentrating.

Twenty-nine of the patients who were free from symptoms, and who were fully employed at the time of the follow-up, had suffered from headache, dizziness, nervousness, or difficulty in concentrating during some period since their final discharge. These symptoms had not been severe enough to cause the patients to stop work, and only a few of them had consulted a physician.

The 48 patients (19%) who after their return to duty had been troubled by headache, dizziness, anxiety, nervousness, or difficulty in concentrating but had shown no real personality changes did not differ from the rest of the series in regard to age. The percentage of women was larger in this group than in the remainder, but the difference was not statistically significant. Pretraumatic mental disturbances and stress situations at the time of the accident were present in 64% and 44% of the cases, respectively. The corresponding figures for the rest of the patients were 44% and 16%. These differences are statistically significant. Many of the patients had had periods of headache, nervousness, etc., before the accident, but since they reported that the symptoms were severer after the accident, we listed the disorders as sequelae of the head injury. Judging from the duration of PTA and the frequency of neurologic disorders and skull fractures, the number of mild injuries was remarkably large.

All eight patients who showed intellectual and/or emotional impairment as a result of the accident had been exposed to severe injuries, with protracted PTA and fracture of the skull. They did not exhibit a higher rate of pretraumatic mental disturbances or stress situations.

Comment

The material is representative of civilian practice at a department of general surgery in a large city. It consists almost entirely of closed injuries. Fifty per cent of the cases resulted from traffic accidents. Eighty-five per cent of the patients received accident compensation. The post-traumatic amnesia lasted at least one hour in 43% of the cases and more than 24 hours in 10%. The corresponding figures in Guttmann's series of civilian cases [12] were 34% and 12%. In Denny-Brown's series,[13] too, the PTA lasted longer than 24 hours in 12%. Fracture of the skull was found in 23% of our patients and in 17% of those in Denny-Brown's series.

Pretraumatic mental disturbances and psychologic stress at the time of the accident were present in 45% and 20% of the patients, respectively. The explanation is that persons who are mentally disturbed or in poor condition caused by stress of various kinds are exposed to accidents oftener than are others.§ In an examination of 200 patients with head injuries, Adler [6] found that only 89 had no history of pretraumatic abnormal personality.

We were responsible for the care of the patients from the first day of hospitalization until their final discharge. The brain surgery, however, was performed by staff members of a trauma service. After the operation the patients were treated according to the same principles as the patients not operated upon. The one of us who was responsible for the patient during the hospital stay was also in charge of the outpatient after-treatment. It is important from the psychotherapeutic point of view that the

§ References 14-16.

entire treatment be in the hands of the same physician.

Early ambulation is important mainly from the psychologic standpoint. Prolonged confinement to bed and inactivity are often a severe mental strain on anxious and nervous patients. Concussioin victims easily fall into a state of emotional tension, with anxiety and restlessness. This is due in great part to the widespread opinion that concussion is a dangerous condition that often leads to persistent or incurable brain damage, with mental illness and invalidism as a result. It is surely unwise to keep a patient of this type in bed for a long period, the more so as we have no proof that brain injuries heal better by this method. A strict regime will confirm the patient's fears. The increased emotional tension, in turn, causes headache and dizziness, which become a new reason for worry, and so on in a vicious circle. If the patient is allowed to move about in bed, to get up soon after the accident, and to return to his occupation after a short time, he will be convinced that his worry about the dangers of concussion and its after-effects was exaggerated.

The post-traumatic tendency to dizziness also appears to be less pronounced in patients who are permitted to be ambulatory soon after the accident. Vertigo is rare, but dizziness is common. The latter symptom is sometimes caused by injuries to the peripheral or central vestibular system. In other cases it may arise from injuries to the vasomotor centers in the brain stem. Psychogenic factors should also be taken into consideration. Reports vary as to the frequency of dizziness, but most workers have found it to vary from 50% to 60%.[7] Only 64 of our patients (25%) had dizziness after the accident. Ten patients had vertigo. In 50 of the cases the dizziness appeared during the first few days in bed, without, however, necessitating a longer stay in bed. In many cases the dizziness quickly regressed as soon as the patient was allowed up.

Approximately half of the patients complained of headache when they regained lucidity. Most of them became free of headache in a few days and were then allowed to be ambulatory. If the headache tended to persist, the patients were urged to get up in spite of the symptom. This had a favorable effect in many cases.

We made a special point of physical activation at an early stage for patients who were nervous, restless, and anxious or who complained of difficulty in concentrating.

The length of the time the patient was bedfast was not dependent on the duration of the amnesia, except that only fully lucid patients were permitted to be ambulatory. Nor was a skull fracture a decisive factor, unless it was compound. In the latter case the patient remained bedfast for one week under preventive treatment with antibiotics. On the other hand, neurologic cerebral focal signs and massive subarachnoid hemorrhage were considered to indicate a prolonged stay in bed. The period in bed after surgery was usually brief.

Early ambulation had no disadvantages. The patients were pleased not to have to be bedfast for a long period. The few who expressed a desire to stay in bed longer than we considered necessary were allowed to do so. These were patients who had been kept in bed for long periods in connection with previous injuries without any post-traumatic symptoms.

The physical activation was always complemented by verbal psychotherapy of a supportive nature. The treatment was begun as soon as the patient became lucid and took the form of relatively brief daily conversations. The purpose was to prevent nervous disturbances or to gain control of any that had already made their appearance. As a rule we achieved our purpose. In some cases nervous symptoms, such as anxiety, restlessness, difficulty in concentrating, and insomnia, could not be checked, or the headache and dizziness did not run the "usual" course. Short-term psychoanalytically oriented therapy was then instituted and continued on an outpatient basis after discharge from the hospital. Almost all these patients had had mental disturbances or had been under

psychologic stress even before the accident.

The risk of a protracted, incapacitating postconcussion syndrome is particularly great among patients who do not respond to simple supportive therapy. The patients with a tendency toward this syndrome can therefore be recognized soon after the accident and can be given more intensive psychiatric treatment.

Dizziness appears to be the symptom in the postconcussion syndrome that is least susceptible to psychotherapy. In itself dizziness usually has no practical consequences in the form of impaired working capacity as long as psychogenic reactions to the symptom can be prevented.

It was our principle to return the patients to full occupation in one stage. For psychologic reasons, it seemed wisest to allow them complete disability as long as the symptoms persisted. This presupposed, of course, that physical activity was maintained and that suitable psychotherapy was administered. Only a very few patients remained under psychotherapy after they had returned to work, and then only for a brief period.

This is not the time to discuss in detail the psychologic background of a postconcussion syndrome. A few observations will, nevertheless, be reported. They conform in general with Adler's [6] findings.

The patient's own memory of the accident or the testimony of witnesses not infrequently gives rise to a state of anxiety, with strong masochistic impulses. It may be difficult for the patient to face the situation consciously. Instead, the experience is relived in anxious dreams and fantasies. In the case of assault the emotional reaction will be especially strong, in contrast to injuries incurred in connection with play or athletics.

The widespread opinion that a head injury is a dangerous condition, which usually causes permanent impairment of the mental functions, leads to mental illness, or later in life gives rise to brain tumors, has great dynamic force. Fantasies about the subject are common. We should bear in mind that in our civilization we have an inordinate admiration for intellectual achievements. A head injury thus comes to have much greater emotional significance than, for example, an injury to an extremity. The patients become "head-conscious."[17]

Patients who are under psychologic stress at the time of the accident often have a desire to get out of their difficulties by exploiting the head injury and its after-effects. In this way they can gain not inconsiderable benefit from the disability. The accident is opportune and is used to advantage by the patient. It should be added, however, that this mechanism was never a conscious one in our patients.

Compensation and litigation in connection with the accident were of negligible importance in the development of mental symptoms in our series. These questions presumably do not come into the foreground until after the post-traumatic symptoms have persisted for some time, bringing with them financial difficulties, considerations of prestige, etc.

The period of disability was at most four weeks in 79% of the 234 patients who had not incurred severe extracranial injuries. Only nine of the patients (4%) were still disabled after eight weeks. Five of these had severe head injuries, and the long period of disability was due to neurologic signs and mental impairment. The remaining four had relatively mild injuries. They showed no neurologic signs, and the long disability originated in environmental factors and pretraumatic personality disturbances.

The age of the patient had no effect on the duration of the disability, although this is a factor that is usually considered to be of prognostic significance.[18] On the other hand, the duration of the disability increased with the length of post-traumatic amnesia. The same observation has been made by other workers.‖

Guttmann's [12] and Denny-Brown's [13] series are the most suitable for a comparison of therapeutic results. Like our material,

‖ References 12, 13, 18.

their cases represented civilian injuries, and the degree of severity, evaluated on the basis of PTA, was about the same.

Twenty per cent of the 170 patients in Denny-Brown's material were disabled for more than two months; 14 patients for more than six months. Guttmann described the course of the disability in 121 cases. Twenty-five per cent of his patients were unable to work two months after the accident, and eight cases were still incapacitated after six months. Guttmann stated that he prescribed early physical activation, with only a brief pereiod in bed.

Müller [19] studied the records of an insurance company concerning 531 cases of head injuries, in which the patients had been hospitalized and given conservative treatment, during the years 1949 to 1950. He found that 35% had been disabled for more than eight weeks and that working capacity was still impaired one year after the accident in 9%.

We conducted a follow-up on an average of one year after the patients had been discharged as cured. With only one or two exceptions, we had not been in contact with any of the patients in the intervening period. There was thus no question of continuous supportive therapy.

Nineteen patients (8%) complained of headache, dizziness, nervousness, anxiety, or difficulty in concentrating. Nevertheless, none of the patients had been disabled a second time or compelled to find less strenuous employment because of these symptoms. One patient's working capacity was impaired after the discharge (Case 7). Russell [17] conducted a follow-up on 200 cases of head injury 18 months after the accident. Forty per cent still had symptoms of the kind in question. In Cedermark's material,[20] consisting of 1570 patients, the frequency was 24% after three years.

There was impaired working capacity due to the head injury in a further two cases in our series (Cases 2 and 3), but in both the cause was neurologic signs and mental deterioration.

Judging by the loss of working time and the frequency of post-traumatic symptoms, the results in the present series represent a great improvement over those published hitherto. Persistent symptoms of the type that make up the postconcussion syndrome were mild and did not have an adverse effect on working capacity, with the exception of one case, in which the treatment was not carried out satisfactorily. The frequency of permanent disability can thus be reduced to the limit determined by neurologic disorders and mental deterioration. Since permanent disability following closed head injury is due to these causes in only a few cases,[13] the prognosis in these injuries is much more favorable than was formerly believed.

The concept of the postconcussion syndrome as chiefly a psychogenic condition finds strong support in the good preventive effects of psychotherapy.

Summary and Conclusions

The material consists of 258 consecutive cases admitted to Serafimerlasarettet in Stockholm for acute head injury. The majority of the injuries were incurred in traffic accidents. The patients ranged in age from 13 to 79 years.

The post-traumatic amnesia lasted for at least one hour in 43% of the cases and for more than 24 hours in 10%. There was fracture of the skull in 23% of the cases.

The patients were kept in bed for one day after the accident. They were then allowed to get up on the condition that they were lucid and no longer complained of severe headache or dizziness. Physical activation was instituted especially early in cases with nervous disturbances. The duration of amnesia did not determine the bedfast period. Nor were skull fractures decisive in this respect, unless they were compound. Prolonged stay in bed was prescribed only in cases of massive subarachnoid hemorrhage and in some cases of neurologic cerebral focal signs. Fifty-three per cent of the patients were ambulatory on the second to fourth day after the accident. Twelve per cent were bedfast for more than one week.

Verbal psychotherapy was begun as soon as the patients became lucid; in most cases it was purely supportive. In 44 cases, however, short-term psychoanalytically oriented therapy was carried out. These were cases in which the risk of a postconcussion syndrome was considered to be great.

The maximum period of disability was four weeks in 79% of the 234 patients who had not suffered severe extracranial injuries. Only nine patients (4%) were disabled longer than eight weeks. The duration of the disabiity increased in proportion to the duration of post-traumatic amnesia. It was not, on the other hand, related to either the age of the patient or the rate of compensation.

None of the 24 patients with severe extracranial injuries had signs or symptoms of the head injury for longer than eight weeks.

The patients were followed up on an average of one year after their final discharge. Only three patients had impaired working capacity as a result of the head injury. This was due in two of them to neurologic disorders and mental deterioration. None of the other patients had been disabled after discharge or compelled to change to a less strenuous occupation. Six of them showed mild personality changes, however, but no real symptoms. Two had had epileptic attacks. Nineteen patients (8%) complained of mild symptoms in the form of headache, dizziness, anxiety, nervousness, or difficulty in concentrating.

The postconcussion syndrome can be prevented in most cases by early ambulation and psychotherapy. Psychotherapy is indicated for a manifest postconcussion syndrome and should be instituted early. The symptoms will then soon disappear or will at least regress to the point that they do not affect the patient's working capacity.

Psychogenic mechanisms are decisive in the origin of a postconcussion syndrome.

REFERENCES

1. Denny-Brown, D.: The Sequelae of War Head Injuries, New England J. Med. 227:771-779 and 813-821, 1942.
2. Guttmann, E.: Postcontusional Headache, Lancet 1:10-12, 1943.
3. Symonds, C. P., and Russell, W. R.: Accidental Head Injuries: Prognosis in Service Patients, Lancet 1:7-10, 1943.
4. Brenner, C.; Friedman, A. P.; Merritt, H. H., and Denny-Brown, D.: Post-Traumatic Headache, J. Neurosurg. 1:379-391, 1944.
5. Ross, W. D., and McNaughton, F. L.: Head Injury, Arch. Neurol. & Psychiat. 52:255-269, 1944.
6. Adler, A.: Mental Symptoms Following Head Injury, Arch. Neurol. & Psychiat. 53:34-43, 1945.
7. Friedman, A. P.; Brenner, C., and Denny-Brown, D.: Post-Traumatic Vertigo and Dizziness, J. Neurosurg. 2:36-46, 1945.
8. Ruesch, J., and Bowman, K. M.: Prolonged Post-Traumatic Syndromes Following Head Injury, Am. J. Psychiat. 102:145-163, 1945.
9. Simons, D. J., and Wolff, H. G.: Studies on Headache: Mechanisms of Chronic Traumatic Headache, Psychosom. Med. 8:227-242, 1946.
10. McKenzie, K. G.: One Aspect of the Posttraumatic Syndrome in Craniocerebral Injuries, Tr. Am. Neurol. A. 69:103-105, 1943.
11. Sheaburn, E. W., and Mulford, E. H.: Ambulatory Treatment of Cerebral Concussion, Bull. Army M. Dept. 69:36-41, 1943.
12. Guttmann, E.: The Prognosis in Civilian Head Injuries, Brit. M. J. 1:94-96, 1943.
13. Denny-Brown, D.: Disability Arising from Closed Head Injury, J. A. M. A. 127:429-436, 1945.
14. Lewis, A.: Discussion on Differential Diagnosis and Treatment of Post-Contusional States, Proc. Roy. Soc. Med. 35:607-614, 1942.
15. Ruesch, J.; Harris, R. E., and Bowman, K. M.: Pre- and Post-Traumatic Personality in Head Injuries, A. Res. Nerv. Ment. Dis., Proc. (1943) 24:507-539, 1945.
16. Dalsgaard-Nielsen, T., and Dirksen, Hj.: Head Injury and Accident-Proneness, Acta psychiat. et neurol. 29:28-29, 1954.
17. Russell, W. R.: Medical Aspects of Head Injury, Brit. M. J. 2:521-523, 1942.
18. Russell, W. R.: The After-Effects of Head Injury, Edinburgh M. J. 41:129-141, 1934.
19. Müller, R.: The Prognosis of Closed Head Injuries, Nord. med. 53:677-681, 1955.
20. Cedermark, J.: Über Verlauf, Symptomatologie und Prognose kraniozerebraler Verletzungen, Acta chir. scandinav. (Supp. 75), 86:1, 1942.

Lipoprotein Patterns of Spinal Fluid Obtained by Paper Electrophoresis

JAMES K. SMITH, M.D.
BRUNO GERSTL, M.D.
WILLIAM E. DAVIS, M.S.
and
DOROTHY L. ORTH, B.A., Oakland, Calif.

Introduction

Recent studies of lipids in multiple sclerosis derive from at least two lines of thought, which may perhaps eventually converge. One is the theory that a fault in lipid metabolism may be involved. Swank * is one of the proponents of this argument, and he has extended his theory into practice by advocating a low-fat diet. Other investigations on the serum lipids in multiple sclerosis, however, have agreed in finding little evidence for a quantitative abnormality in the cholesterol, phospholipids, or lipoproteins.† The second approach is based on the search for breakdown products of myelin in the spinal fluid. Myelin is a lipoprotein complex whose exact chemical analysis has not yet been accomplished. One possible way to find out how the myelin is destroyed would be to identify its breakdown products. This, then, would offer some indication as to location or type of bond which had been disrupted. The present study constitutes a tentative approach to this, using the technique of electrophoresis as applied to spinal fluids from multiple sclerosis and other diseases of the nervous system in which there is breakdown of nerve tissue.

Received for publication March 6, 1956.
From the Neurology and Laboratory Services, Veterans Administration Hospital.
This investigation was supported by Grant No. 92 from the National Multiple Sclerosis Society.

* References 1, 2.

† References 3-5.

Aird, Gofman, and associates [6] were unable to find significant amounts of lipoproteins in the spinal fluid with the ultracentrifuge. Baudouin,[7] however, using paper electrophoresis, described small amounts of material (obtained after concentrating the spinal fluid) that took a lipid stain and moved in two components—one corresponding to the α-lipoprotein of the serum and the other moving more rapidly. These findings were apparently made on normal fluids, and the authors do not indicate whether they had applied the technique to a study of disease states. Several reports in the older literature by workers using chemical techniques indicate that lipid material can be demonstrated in the spinal fluid both in pathological conditions and (in smaller amounts) as a normal finding. The lipids so studied have included fatty acids,[8] cholesterol,[9] and phospholipids.[10]

It may be noted that discrepancies between amounts of lipids found in spinal fluid and in blood serum have been reported by various workers. Katzenelbogen,[11] citing the work of Plaut and Rudy on cholesterol, emphasized that the cerebrospinal fluid content of this material may be elevated while its concentration in the blood is low and the blood-spinal fluid barrier of normal permeability. Hence it is not unreasonable to anticipate that a demyelinating disease may be accompanied by an increase of lipid material in the spinal fluid without necessarily any change in the blood lipids.

In the course of the present investigation, the lipoprotein levels of the blood serum were determined, as well as those of the spinal fluid. Our findings, like those of Roboz and others, indicate no significant abnormality in the serum pattern, and this

report, therefore, concerns itself solely with the spinal fluid.

Material

Spinal fluids were obtained by lumbar puncture from a group of patients with various neurological disorders and from a few normal subjects. Included were 21 patients with multiple sclerosis, from several of whom it was possible to obtain repeated samples at intervals. An attempt was made to classify the patients in this group as clinically "active" or "inactive," the criteria for activity consisting in the history or observation of an acute exacerbation or obvious progression of disability within a three-month period prior to the time that the spinal fluid specimen was obtained.

Methods

The spinal fluids were concentrated by dialysis in collodion bags under negative pressure at 0 to 1 C, as recommended by Mies.[12] The almost dry concentrate was taken up in a small measured amount of 0.85% saline. Horizontal paper electrophoresis was carried out on a box-type apparatus at room temperature, using Whatman No. 1 filter paper and 0.06 M barbital (Veronal) buffer. The potential was 7.1 to 7.2 volts per centimeter, current 1 ma. per 1 cm. width of paper strip. Migration was allowed for five and one-half hours. For demonstration of the proteins, amounts of concentrate corresponding to 0.12 to 0.45 ml. of spinal fluid, and for that of lipoproteins about 10 times this amount, were placed on the filter paper. After

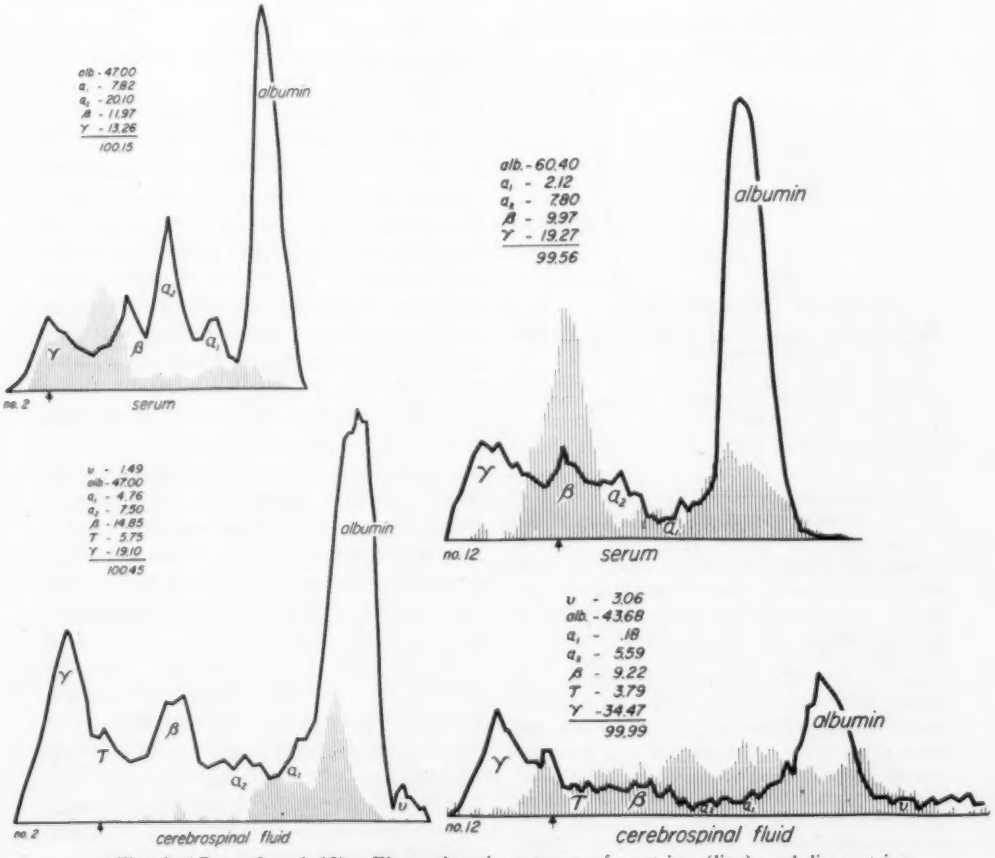


Fig. 1 (Cases 2 and 12).—Electrophoretic patterns of proteins (line) and lipoproteins (shaded area) in serum and cerebrospinal fluid from two cases of actively progressive, well-advanced multiple sclerosis. Note the peak in spinal fluid lipoprotein of Case 2, corresponding to the albumin component of the protein.

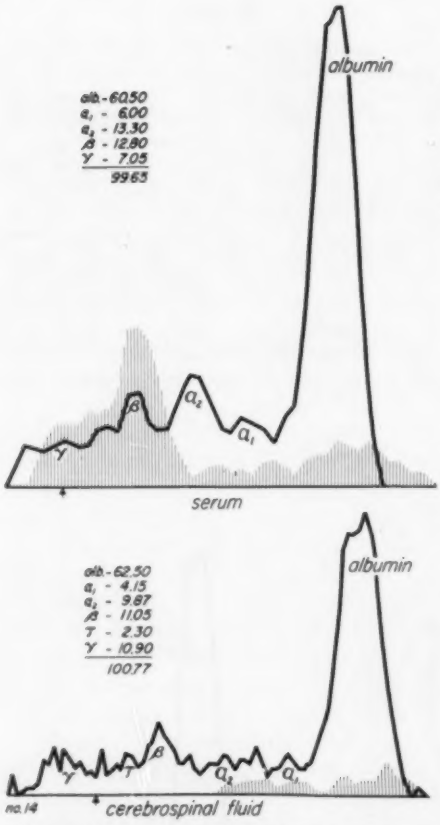


Fig. 2 (Case 14).—Electrophoretic pattern of proteins (line) and lipoproteins (shaded area) in serum and cerebrospinal fluid from a case of chronic paraplegia secondary to hemangioma of the spinal cord.

completion of electrophoresis, the strips were dried for 10 minutes at 100 C. Bromophenol blue (tetrabromophenolsulfonphthalein) was employed for staining the proteins and oil red O for staining the lipoproteins (Kunkel and Slater[18]). Oil red O was made up as a stock solution of 4.8 mg. per 100 cc. in absolute alcohol (ethanol). This was diluted to give a 0.04 mg. per 100 cc. solution in 50% alcohol on the day staining was carried out. This resulted in a minimal background staining. The same batch of dye was used for all experiments. The strips were placed in a covered glass dish containing the oil red O solution for 16 hours at room temperature and stained under constant slow shaking. The stained strips were washed twice in water and dried. Densitometry was done on a Photovolt apparatus, Model 5018A, using a filter with maximum transmittance at 600 mμ for the bromophenol-blue-stained strips and one with 515 mμ for the oil-red-O-stained strips. On two occasions, human serum diluted 1:200 and concentrated in the same way as the spinal fluids was subjected to electrophoresis, with undiluted serum serving as control. Both the protein and the lipoprotein curves were almost identical before and after concentration, indicating that the procedure employed here did not produce any change in electrophoretic mobility.

Results

In 41 of 54 specimens from the multiple sclerosis group and in 30 of 32 fluids from patients with other central nervous system diseases a positive test for lipoprotein was obtained; that is, a material appeared which combined with a fat stain (oil red O) and which also moved in the electrophoretic field with the mobility characteristic of a protein molecule. Inasmuch as lipoproteins do not combine with fat stains in a perfectly stoichometric fashion, it is not feasible to speak here of quantity. However, we wish to call attention particularly to the finding in several of the fluids of a distinct peak of lipoprotein (Fig. 1, *no. 2*) in the area corresponding to the albumin component of the protein pattern of the spinal fluid. This occurred in six of the multiple sclerosis series, all of which were clinically classified as actively progressing and severely disabled cases. This type of curve also was found in seven fluids from the group of miscellaneous central nervous system disorders, including syphilis of the central nervous system, recent cerebral infarction, post-traumatic encephalopathy, "hepatitic encephalopathy," and severe neuropathy of cranial nerves in a diabetic. It was never found in the fluid from normal persons or those with mild or inactive neurological disease.

Besides the distinctive curve just described, the commonest lipoprotein pattern seen was an irregular diffusion throughout the area of globulins and into the albumin without any definite peak (Fig. 1, *no. 12*). Rarely a third pattern was observed, namely, a sharp peak in the globulin zone. This was in the β-globulin zone in four instances and in the α-globulin zone once. It may be significant that in the cases showing a peak in

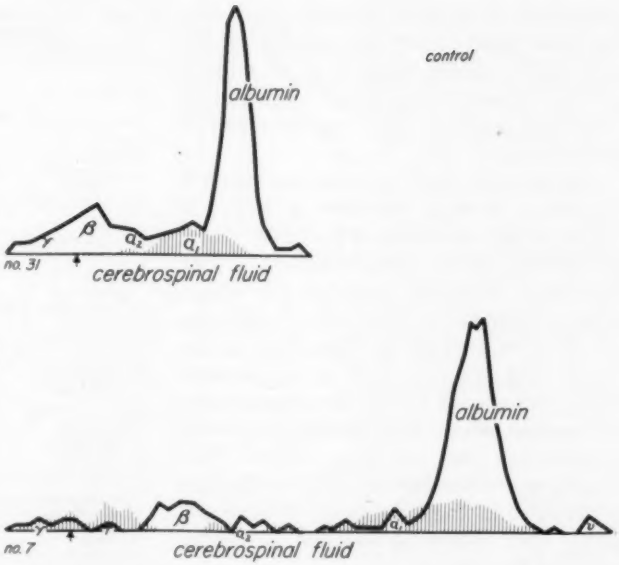


Fig. 3.—Electrophoretic pattern of proteins (line) and lipoproteins (shaded area) from cerebrospinal fluid of a case (No. 31) of anxiety neurosis with no clinical or laboratory evidence of organic neurological disease, and a case (No. 7) of idiopathic grand mal studied three weeks after his most recent seizure.

the β-globulin area there was pleocytosis of the spinal fluid.‡

Fluids were obtained from four patients who had neither a history nor findings of neurological disease and from five additional patients who were presumed to have no active neurological disease (three with idiopathic epilepsy studied in an interval phase without history of recent attacks, one with residuals of a childhood attack of poliomyelitis, and one with residuals of an old disc syndrome). In all these cases the spinal fluids, including the γ-globulin were entirely normal. Among these nine "control" fluids, one showed no lipoprotein whatever, five had faint traces, and three had the characteristic low or flat pattern, which was the commonest type seen (Fig. 3). It is suggested, therefore, that the presence of lipoprotein in the spinal fluid is in itself not an abnormal finding.

We wished, however, to see how the presence or absence of this spinal fluid lipoprotein would obtain in the group of multiple sclerosis patients, several of whom were studied in this respect at repeated intervals (three months apart). Table 1 represents the sum total of these determinations, along with other spinal fluid data, each of which is correlated with clinical assessment of activity and severity of the disease at the time the fluid was obtained.

It appears from this Table that lipoprotein is correlated with activity and severity of disease in approximately the same degree as is the γ-globulin. However, Table 2 shows in a few selected, but representative, examples that in individual cases the lipoprotein may be quite variable in its appearance. Thus, in Case C it is not found during an active phase of the disease (8/18/55), and it is present during a remission in Case A(3/9/55). We studied all such cases of multiple sclerosis in which serial samples were obtained and did not find that the presence or absence of lipoprotein in the spinal fluid showed a consistent correlation with the activity of the disease or its severity.

Comment

The present work confirms the observation of Baudouin that lipoprotein can be

‡ One of these was a case of multiple sclerosis; the others from two cases of chronic meningoencephalitis, etiology undetermined.

demonstrated by electrophoresis in the cerebrospinal fluid. From the findings of this material in normal subjects or in subjects without manifest clinical activity, it can be concluded that lipoprotein may be a normal constituent.

Furthermore, there was no demonstrable correlation between presence of this substance in the cerebrospinal fluid and "activity" of the disease multiple sclerosis. It does not seem justifiable, therefore, to assign either diagnostic or prognostic significance to the mere presence of lipoprotein in the spinal fluid. Further work is contemplated which will attempt to make semiquantitative estimations by elution of the dye-lipoprotein combination from the paper strips. This should make it possible to determine whether a quantitative threshold exists between the spinal fluid of normal and that of disease states in this regard.

The other finding we wish to emphasize is the pattern in some cases with active breakdown of nerve tissue of a peak in the lipoprotein corresponding to the albumin component of the spinal fluid proteins. This distinctive configuration was never seen in normal subjects or in persons with inactive disease. Its occurrence in 13 of the total number of reported examinations (86) is relatively small, of course. An attempt to identify the nature of this substance is contemplated. Until its identity can be definitely determined, it is only speculative to propose the question as to whether it represents a phase in the catabolism of myelin.

We are unable to state why the lipoprotein shows so little consistency in its occurrence within the same subject at different times, or why the "albumin" lipoprotein was found so infrequently. However, a theoretical explanation may be offered. This is simply that lipoprotein complexes resulting from the breakdown of myelin may be unstable, perhaps constantly undergoing further enzymatic resolution into simpler components, until the last linkage between a protein and a lipid type of molecule is dissolved. At this point no lipoprotein would be demonstrated

TABLE 1.—*Clinical Classification in a Series of Multiple Sclerosis Patients* *

	Activity		Disability	
	Active	Inactive	Severe	Mild
Colloidal gold				
Abnormal	19	6	22	3
Normal	17	12	18	11
Protein				
Abnormal	25	5	22	8
Normal	12	12	18	6
Cell Count				
Abnormal	11	4	9	5
Normal	26	13	31	9
γ-Globulin				
Abnormal	22	9	30	1
Normal	16	7	10	13
Lipoprotein				
Present	28	13	32	9
Absent	8	5	8	5

* The results of 54 examinations of the spinal fluid (from 21 patients) are here set against two sets of clinical estimates of the condition of the patient at the time the specimen was obtained. The cases classified as "active" have shown evidence of new lesions or progression of existing disability within three months of the date the specimen was taken, whereas the "inactive" group showed no such evidence. Those classified as "severe" are patients judged as above a 4 on the 1-10 score devised by Kurtzke,[14] while 4 or below constitutes "mild" disability.

The colloidal gold curve is considered definitely abnormal here if it includes at least one Grade 3 precipitation in any one of the tubes. The upper limit of normal for the protein was taken as 45 mg. per 100 cc., that of the cell count as 5, and that of the γ-globulin as 13% of total protein.

TABLE 2.—*Serial Determinations on Spinal Fluid of Three Patients with Multiple Sclerosis* *

Case	Date	Lipoprotein	Disability Score	Clinical Status	Cells /Cu. Mm.	Protein, Mg./100 Cc.	Gold Curve	Gamma Globulin, % of Total Protein
A	3/ 9/55	Present	6	Stationary	12	35	1233321000	25
	6/10/55	Absent	6	Stationary	4	38	1233332100	22
	9/10/55	Present	6	Active	3	59	0011000000	25
	12/10/55	Present	6	Active	1	39	1223210000	20
B	3/ 8/55	Present	7	Active	19	34	5554310000	34
	6/ 9/55	Absent	7	Active	4	54	5543210000	38
C	8/18/55	Absent	7	Active	2	81	1222111100	13
	11/17/55	Present	6	Active	5	73	0001110000	15

* These findings illustrate how presence or absence of lipoprotein may vary without any apparent relationship to clinical state or other spinal fluid findings.

by electrophoresis. At a certain stage in the disease this breakdown by ferments might be progressing very rapidly; at another stage, more slowly. Both the quantity and the configuration of lipoproteins seen might thus vary at different times in the same subject and in the same clinical stage of disease.

Summary

Lipoprotein has been demonstrated in the spinal fluid of normal subjects and of patients with a variety of neurological diseases.

A characteristic configuration of a lipoprotein component that shows the mobility of albumin is described, and it is believed that its occurrence in cases of rather marked tissue breakdown is significant. It is suggested that it may be derived from catabolism of nerve elements, though this can only be established by further investigation.

REFERENCES

1. Swank, R. L.: Treatment of Multiple Sclerosis with Low Fat Diet, A. M. A. Arch. Neurol. & Psychiat. 69:91 (Jan.) 1953.

2. Swank, R. L.: Blood Plasma in Multiple Sclerosis, A. M. A. Arch. Neurol. & Psychiat. 69:281 (March) 1953.

3. Chiavacci, L. V., and Sperry, W. M.: Concentration of Cholesterol and of Lipid Phosphorus in Blood Serum in Multiple Sclerosis, A. M. A. Arch. Neurol. & Psychiat. 68:37, 1952.

4. Bernsohn, J., and Namajuska, I.: Phospholipid Fractions in Multiple Sclerosis and Normal Serum, Proc. Soc. Exper. Biol. 88:124 (Jan.) 1955.

5. Roboz, E.; Hess, W. C.; Foster, F. M., and Temple, D. M.: Serum Lipid Studies in Multiple Sclerosis, A. M. A. Arch. Neurol. & Psychiat. 72:154, 1954.

6. Aird, R. B.; Gofman, J. W.; Jones, H. B.; Campbell, M. D., and Garoutte, B.: Ultracentrifuge Studies of Lipoproteins in Multiple Sclerosis, Neurology 3:22 (Jan.) 1953.

7. Baudouin, A.; Lewis, J., and Hillion, P.: Paper Electrophoresis of Spinal Fluid Proteins: Study of the Lipoproteins, Compt. rend. Soc. biol. 147:1036 (Jan.-June) 1953.

8. Knauer, H., and Heidrich, L.: Spinal Fluid Lipids, Ztschr. ges. Neurol. u. Psychiat. 136:483, 1931.

9. Plaut, F., and Rudy, H.: Study of the Spinal Fluid Cholesterol Content, Ztschr. ges. Neurol. u. Psychiat. 146:229, 1933.

10. Lafontaine, A., and van Gehuchten, P.: The Phospholipids in the Course of Certain Human Nervous Diseases, J. belge neurol. & psychiat. 44-46:344, 1946.

11. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1935.

12. Mies, H. J.: Paper Electrophoresis of Spinal Fluid, Klin. Wchnschr. 31:159, 1953.

13. Kunkel, H. G., and Slater, R. J.: Lipoprotein Patterns of Serum Obtained by Zone Electrophoresis, J. Clin. Invest. 31:677, 1952.

14. Kurtzke, J. F.: A New Scale for Evaluating Disability in Multiple Sclerosis, Neurology 5:580 (Aug.) 1955.

15. Jencks, W. P., and Durrum, E. L.: Paper Electrophoresis as a Quantitative Method: The Staining of Serum Lipoproteins, J. Clin. Invest. 34:1437, 1955.

16. Bucher, T.; Matzelt D., and Pette, D.: Paper Electrophoresis of Cerebrospinal Fluid, Klin. Wchnschr. 30:325, 1952.

17. Durrum, E. L.: Microelectrophoretic and Microionophoretic Technique, J. Am. Chem. Soc. 72:2943, 1950.

18. Durrum, E. L.; Paul, M. H., and Smith, E. R.: Lipid Detection in Paper Electrophoresis, Science 116:428, 1952.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Dr. Erich Lindemann, M.D., Presiding
Regular Meeting, Jan. 19, 1956

Studies on the Stability of Interaction Patterns in Psychiatric Interviews. Dr. George Saslow, Boston, and Dr. Joseph D. Matarazzo.

Problem.—To investigate the stability (reliability) of patients' interaction patterns in repeat interviews with the same or with a different interviewer.

Subjects Used.—Three experiments were done in all. The first was a test-retest study in which 20 psychiatric outpatients were each interviewed in the same afternoon independently by two different interviewers. The second study was a test-retest experiment in which 20 other patients were each interviewed twice, one week apart, by the same interviewer. The third study was a repetition of the first experiment, using still another group of 20 patients.

Procedure.—The method of observation and measurement used was the Chapple interaction chronograph. This instrument, which is activated by an observer on the other side of a one-way screen, permits the continuous measurement (in time units) of such patient-and-doctor interaction variables as number of units of interaction, duration of each interaction, frequency of initiative taking, frequency of interruption, duration of interruption, and frequency of dominances and submissions—all obtained during the course of a highly systematized (though free-appearing) and relatively standardized psychiatric interview. The average duration of the interview is 32 minutes.

Results.—The interaction patterns in the two interviews of a given patient in the three studies were almost identical, with test-retest reliabilities ranging from 0.72 to 0.96 for the 10 interaction variables studied. Thus, invariance of interaction pattern was demonstrated when interview conditions were standardized. Furthermore, there was demonstrated a very striking relationship between the interaction pattern of the interviewer and the pattern elicited from the patient. Thus, changeability with planned changes in stimulus conditions (variance of interaction patterns) was also demonstrated.

Conclusions.—Raines and Rohrer most recently have confirmed what other investigators have been reporting for years, i. e., the low reliability between two psychiatric interviewers when each sees a given patient independently and then makes a rating of the patient's level of anxiety, interpersonal skills, etc. Findings of the three studies discussed above indicate that high reliability between interviewers is possible if one standardizes somewhat the stimulus conditions (i. e., the interviewer's behavior), as well as defining the patient characteristics (responses) under study.

Discussion

Dr. Erich Lindemann.—The methodology in interview analysis is open for discussion. When I learned my psychiatry in Germany, there was much talk of content analysis in interviews. You were worried that the interviewer was likely to underestimate variations in the formal aspects of the interview. Here a precise type of measurement is being introduced which may be useful in distinguishing minor variations from patient to patient and from condition to condition. From the material, by implication, is there a high degree of observer reliability?

Dr. Alfred H. Stanton, Belmont, Mass.: This research program is a quite interesting one—the authors have documented their point and demonstrated another behavioral regularity quite thoroughly. This means that they have worked out another route for checking the inferences we usually make upon the basis of the content of the interview. The more

alternative ways of checking such inferences we have, the more weight we are entitled to give to the inferences.

If, now, we proceed to the question of what the relationship of their observations is to the content of the interview—to the patient's reports about himself and his environment as he perceives it—there are two points to be noted. First, this study is in a stronger position than many in that the variables the authors have treated quantitatively are variables which are pertinent to the type of material of interest to psychotherapists—dominance and submission, for instance—and they should have less trouble than is often the case in trying to work out the relationship between their observations and clinical considerations. It is, nevertheless, a very difficult extension of the work, and I think we should be glad that it is on their program.

DR. JOSEPH D. MATARAZZO: Dr. Jean Phillips has spent a year and a half reviewing the literature of content analysis and has communicated with people who have wrestled with this problem. It is a difficult problem. She has had to work out a method. In combining several, she has a workable tool.

DR. JEAN PHILLIPS: I think using several systems is the answer. Topic (content) will be studied, but as related to temporal (interaction behavior) analysis. With dominance and submission as inferred from "content," one should see whether this is related to behavior as measured in a real "dominance-submission" sequence of a standardized interview.

DR. JOSEPH D. MATARAZZO: We found that some of our patients in the first interview would talk about marital relationships, some about military experience. Even though the content differed, they were apparently the same persons by interaction chronograph measurement.

Neuropsychiatric Aspects of Acute Poliomyelitis. DR. MARTIN R. COLES, Belmont, and DR. JIMMIE C. BROCKMAN, Buffalo.

This study was designed to investigate the delirium occurring with acute poliomyelitis, the psychological impact of an acute, major, and crippling illness, and the possible role of the psychiatrist in this type of medical crisis. A series of 101 adult patients with acute poliomyelitis were studied, of whom 46 were in respirators. Seventeen cases of delirium were observed. This was characterized clinically by a varying level of consciousness, pleasurable hallucinatory experiences, and frequent illusions and delusions. The imaginary experiences were frequently described by the patient as "wakeful dreams." There was waxing and waning of the degree of disorientation and confusion, with a shortened attention span. This picture lasted from a few days to several weeks, occurring initially with the febrile phase and in the patients with signs of bulbar involvement. This delirium markedly resembles the peduncular hallucinosis described by Lhermitte in 1922.

A general study of the psychological response of patients to acute poliomyelitis revealed certain predominant patterns. Denial was seen in the majority of patients, and its degree seemed to bear a direct relationship to the severity of their illness. For patients in the respirators, denial was a universal reaction and was responsible for a sense of well-being and confidence, at startling variance with the facts. Other mechanisms observed were rationalization, regression, paranoid responses, and aggression. Depression was surprisingly infrequently observed in the acute phase.

Discussion

DR. RAYMOND D. ADAMS: We all appreciate the accuracy of Dr. Brockman's observations on these cases. Knowing a little about the literature, I should say the accurate recording of such cases is worth while. So little is good on delirium in medical writings. I should have said that the authors reported that delirium was quite frequent, as well as unexplained comas and other types of "encephalitis." In this state of delirium and its components, I would include tremulousness, motor restlessness, psychic overactivity, a stereotype of psychic reaction, confusion, sleeplessness, sensorial difficulty, and convulsions. I think this represents a unique clinical state. It should be distinguished from a confusional psychosis, where the sensorial component is not predominant. This delirium syndrome does occur in poliomyelitis and in a number of other conditions, such as drug intoxication, withdrawal states, and systemic infections. It must be obvious that it represents some type of brain disease, but no one knows what kind of trouble or where it is situated. All of these we are searching for and case

material is worth the most careful analysis. The description by Lhermitte has been mentioned. He has done most to advance the idea that visual hallucinatory states could be produced not by something wrong at the end-organ, or cortex, but by a lesion in the midbrain. If one looked carefully at some of his cases and examined some of these patients on the neurological wards, one would be in doubt as to whether the pathology is in the midbrain. Something can happen with thalamus, mesencephalic area, creating visual hallucinations in which the patient has insight and reasonable mental clarity. The best material is the vascular case, where a neat lesion can be traced. We have had a few such cases. The pathology of the thalamus and its anatomy are so complicated that it is hard to work out a uniform picture. We have five of the cases that Dr. Brockman has described in our pathological material. I think it would be worth while to go through this material with care, comparing these 5 cases with the other 19 or 20. The anoxia factor, shock, circulatory disorder, and fever get involved, so it is not a simple problem. How many of your patients had tactile and auditory hallunications? They were mentioned by Lhermitte in his cases. We have seen auditory illusions and hallucinations with lesions of the lower brain stem. I suspect some secondary auditory fiber systems are getting involved. Lhermitte's cases were in a higher part of the brain stem. What Dr. Coles tells us about the psychological reaction is known to all clinicians who have to deal with the disease. Some of the patients are scared to death, and families even more so, sometimes unduly. I would not say that all patients who go into a respirator are euphoric. One of our problems is to get them calmed down. Sometimes what Dr. Brockman has seen is the result of persuasive management by the house staff. Doctors think patients should be more worried than they are. That is true in tuberculosis, vascular diseases, etc. What this denial is, I do not know. Sometimes it is a lack of appreciation of what they are up against, sometimes a type of psychological defense to keep them from being too much upset by it.

Dr. Joseph M. Foley: Dr. Mendelsohn, a house officer on the Tufts medical service at the Boston City Hospital, and I made independent observations on some patients in the respirator, and lately we have been comparing notes. Several features of this psychotic reaction are of interest. Anoxia alone cannot produce it. We had patients who were anoxic for days before going into the respirator who had no such symptoms. The reaction occurred after they had been in the lung for four to seven days, and it lasted 11 to 14 days. Although it is true that the content was not horrendous, neither was it always pleasant. Some of our patients showed a good deal of aggression and resentment.

A very striking feature to us has been the vividness of the patient's memory of these unreal experiences, often when there was no memory of the reality situation. This vividness of memory does not persist after the ordinary dream or after delirium.

I would agree with Dr. Adams that this psychotic reaction is different from Lhermitte's peduncular hallucinosis. Dr. Mendelsohn and I have wondered whether it may not be a physiological disorder, occurring as a manifestation of sensory deprivation, since in the mechanical respirator there is a relative poverty of movement, an isolation of the head from the body, and a hypnotic similarity of visual and auditory experiences. What we are seeing may be a modification of Hebb's experiments in sensory deprivation.

Dr. Robert Arnot: What if you put a nonpoliomyelitis patient in a respirator? The body is pleasantly warm, and there is a motor running. So many of these polio patients thought they were in a motor boat or an automobile. If you put a normal person in a respirator for a period of time, wouldn't he take a trip in that semiconscious state? He would be lying there 24 hours. He would be drifting off to sleep at times.

Dr. Jimmie C. Brockman, St. Louis: We did not feel that we saw any frank auditory hallucinations. Auditory illusions were frequent, apparently as the result of misinterpreting noises of the environment. We did wonder whether the motor of the respirator was responsible for the motor trips. I agree with Dr. Adams that the etiology is something about which we can only surmise. We did see these patients daily, for about six weeks, at times when they seemed clear and at other times when they were disoriented. We were impressed by the vivid recollection they had. As they began to recover, they had some concern about what this meant. Did this mean that they were temporarily losing their minds? We reassured them that it had been a delirium and that they need not worry about recovery from it. Is the sensory input actually reduced? We considered Hebb's work, and it was our feeling that sensory input is not reduced, since they have a great deal of pain and discomfort, though paralyzed. We think denial is a valuable mechanism to help make an intolerable situation more bearable.

A Psychiatric Study of Attempted Suicide as Seen in a General Hospital. DR. PETER E. SIFNEOS.

The paper dealt with the cases of 155 patients who attempted suicide and were admitted to the Massachusetts General Hospital over a period of nine years.

The findings on the patients fit roughly into the general patterns described in the literature on suicide.

Barbiturate was ingested oftener than any other poison.

The commonest reasons for suicide, as given by the patients and their relatives, were hostility, loss of loved one, environmental manipulation, and reaction to "incurable illness."

In the psychotic patients no clear reasons for suicide were elicited. Their actions seemed impulsive.

In the melange of reasons that were given for the suicidal attempts, two major classifications seemed to stand out: painful emotional state of being, and reactions. In response to environmental conditions, human beings develop painful emotional states. Their unsuccessful reactions (defense mechanisms) progressively intensify their painful emotions and isolate them from their environment. Suicide finally appears the only reaction that seems possible. The patient then attempts suicide.

The word *Autoktonism* is proposed to describe a recognizable state of mind in a patient about to kill himself.

The above pattern is demonstrated specifically in neurotic and psychotic patients, and some ways by which to prevent suicide were discussed.

Critical Ages for Maternal Bereavement in Psychoneuroses. DR. HERBERT BARRY JR.

In a retrospective study of 1000 psychoneurotic patients, deaths of parents during childhood followed a pattern that was different from that of the general population. Death of the mother before the child was 5 years old was more frequent in the case of neurotics: This frequency is reliable at the 0.01 level of confidence. Little girls are more adversely affected than boys, the most vulnerable ages being the first three years. This finding is reliable at the 0.05 level of confidence.

Comparisons with the general population suggest that death of the mother may also be related to neuroses in men. Seven per cent of the females and 4% of the males experienced maternal bereavement during childhood. The vulnerable period extends from birth to 8 years of age.

When other types of separation from parents are included, 12% of the females and 7% of the males were deprived of their mothers at some time during childhood. These findings are similar to previous studies indicating that death of the mother is associated with psychosis or delinquency and that girls are more influenced by parental loss than boys.

Death of the father follows a different pattern. The distribution of paternal deaths for neurotics is more like that for the total population. The term "broken homes" is, therefore, no longer adequate in psychiatry.

Discussion

DR. LEO ALEXANDER: I am very much impressed with Dr. Barry's original and informative study. In our science, in which we deal with so many unsharply defined variables, his ability to quantitate his findings is of great scientific and practical importance. This may also be of importance in medicolegal situations, and I, for one, hope to derive help from Dr. Barry's study. The new German government has taken the very straightforward and very responsible step of assuming responsibility for the acts of the former Nazi government and has asked me to give expert testimony in the case of a young woman who had been exposed to hardships engendered by the defunct Nazi government at an early age, on whether or not these hardships precipitated schizophrenia in this young woman. Dr. Barry's study and similar studies in the future will greatly aid in the evaluation of such questions.

Dr. Wilfred Bloomberg, M.D., President, Presiding
Regular Meeting, Feb. 16, 1956

The Predepressed Personality. DR. ROBERT ARNOT.

"Depressed are the peacemakers" would be a proper subtitle for this paper, which describes the type of personality that gets depressed. Whether the final diagnosis is psycho-

neurosis, manic-depressive, or reactive, the predepressed personalities may be similar. These people want peace at all costs. They fail to settle issues when they arise. They hold in resentments and let them accumulate. They try to be friends with everyone and are highly concerned with what others think of them. They are overly conscientious and perfectionistic. These traits lead them to drive themselves to a state of tension and then fatigue and depression. Their peacemaking, then, is an evidence that a neurosis precedes and participates in the depression.

This type of personality rests on a psychological-physiological disturbance. The desire for peace is an expression of a physiologic make-up that does not tolerate well unpleasant stimuli, such as loud noises. A state of tension exists that is aggravated by many stimuli, of which disturbances in interpersonal relationships are one kind.

Theoretically, a too-sustained cortical-diencephalic relationship produces the neurophysiologic state. The cortex drives on the diencephalon and vice versa. Finally, a state of diencephalic exhaustion is produced. In the earliest phases psychotherapy will break up this cortical driving. Later electric shock may be necessary.

Discussion

DR. PAUL I. YAKOVLEV: Dr. Arnot's portrayal of the "predepressed" personality is based on thoughtful observations, and as a description it is excellent; these are real people whom one knows among patients, acquaintances, and friends. Does he think, however, that a person with this particular make-up is predictably bound to have a "clinical" depression, I doubt it. A tendency to gravitate to certain occupations is an interesting side-line. Dr. Arnot mentioned druggists as often being of the type he referred to as "peacemakers." I would cite carpenters. As I recall those whom I have known, the image of a carpenter to me (at least when dealt with in his own occupational framework) is that of a peaceful, reserved, patient, and judicious person. Is it because Joseph of Nazareth was a carpenter? I cannot say. Be this as it may, the anatomical-physiological interpretations of the "predepressed" personality raise many difficulties, of which Dr. Arnot himself is clearly aware. The attempts to translate the empirical generalization, based, after all, on subjective experience, into the language of anatomy and physiology is always a formidable undertaking. Such attempts are certainly worth while for their own sake; it is a stimulating and useful intellectual exercise. Yet one cannot help being perplexed by the abysmal gap between, say, the "peacemaker" type of personality and a depressive state of mind and the circuits of electrical potential change in the brain. Dr. Arnot mentioned some of the speculative notions which we have exchanged in conversation. Indeed, the concept of Jacksonian "latitudinal" levels of functions superimposed "from below up" has been and remains a most useful working hypothesis for ordering physiological and anatomical facts so long as one remains within the framework of Cartesian causality and logic. However, this concept ceases to be useful as soon as one considers the functions higher than those attributed to the midbrain level. Sir Charles Sherrington explored the functions of the spinal cord and medulla oblongata but threw in the sponge, as it were, when he attempted to reach beyond the midbrain. Ivan Petrovitch Pavlov, a notably irascible man, started from the opposite end—from above, but somehow never reached below the cortex; and we still argue whether the conditioned reflex is more profitably understood as a Cartesian physiological or as an Aristotelian teleological phenomenon? In a perhaps naive hope of finding a generalized theoretical framework which would permit one to define and translate the structure and function of the brain in to terms of needs of living, I have proposed a few years ago the concept of "longitudinal" levels of organization of functions "from within out": from innermost universal, yet intimately private visceral sphere, to species-specific intermediate and not-so-private expressive-emotional sphere, and, finally, to highly individual, outermost, and so inherently public effective transactional sphere of the experience of living. There is abundant evidence that the brain itself developed and is built that way—"from within out." This concept of longitudinal levels, if it be sound and empirically structured, as I think it is, may perhaps be more suitable for statement in the anatomical and physiological terms of what in essence are empirical data, even though they usually are of high degree of abstraction. I appreciate Dr. Arnot's attempt to apply these notions to his interpretation of these data.

DR. HAROLD W. WILLIAMS, Providence, R. I.: This type is a discernible one, separate from other depressions. From the point of view of complaints, these people do not say they are depressed. They complain at length about uncomfortable feelings experienced in the soma which convey to them the idea of a physical illness.

Oxidative and Proteolytic Enzyme Activities in Human Brain Tumors. DR. NORMAN ALLEN, Chapel Hill, N. C., and DR. ALFRED POPE, Belmont, Mass.

The activities of three enzymes have been measured in a series of 15 human brain tumors, using the quantitative histochemical techniques of Linderstrøm-Lang. With this method histological control of the analyses have been accurate and it has been possible to select viable pure samples of tumor types for study. Cytochrome oxidase activities are generally low in all tumors as compared with those of human cortex but are of approximately the order of human white matter. There is a specific difference, however, among types of gliomas. Astrocytomas are very low, whereas glioblastoma multiforme is approximately twice as high. Tumors containing oligodendroglia are also higher than astrocytomas. These data correlate well with previous oxygen-uptake studies done by other workers. Dehydropeptidase I activity is present in the glioma group in a slightly higher level than that of either cortex or white matter. It is somewhat lower in the benign intracranial tumors. L-alanylaminoacetic acid (glycine) dipeptidase is present in gliomas also in a slightly higher level than in either cortex or white matter. The presence of these last two enzymes is taken to reflect a high protein turnover in brain tumors.

Discussion

DR. ALFRED POPE, Belmont, Mass.: May I add a footnote to Dr. Allen's presentation by considering briefly our interest in proteolytic enzymes in glial tumors?

Very little is known about mechanisms for protein synthesis in the brain, but, like other tissues, the brain does contain a group of enzymes capable of catalyzing the hydrolysis of various specific peptide substrates. Homologous peptidases of the alimentary tract can, in some instances, also catalyze transpeptidation reactions and, under certain special equilibrium conditions, the formation of peptide linkages as well. It seems likely that the intracellular proteolytic enzymes of brain have some role in the constant turnover of protein that apparently accompanies both the discharge and the trophic function of neurones. At any rate, the activities of tissue proteolytic enzymes have been rather generally regarded as indicative of rates of protein turnover in many other tissues, and, in general, peptidases show increased activity with neoplasia.

The neurohistological localization of proteolytic enzymes is largely unknown. We have made considerable study of the quantitative histochemistry of the L-alanylglycinease discussed by Dr. Allen in a number of regions of the rat and human nervous systems. The results, particularly those upon its intralaminar distribution in cerebral cortex, indicate that this enzyme resides in the cell bodies of both neurons and neuroglia and probably reflects the amount of actively metabolizing cytoplasmic mass. It is likely that the latter is true of the tumors also, since, although the dipeptidase activity in terms of total or of fat-free solids is about the same in the gliomas as in normal white or gray matter, it is lower if expressed in terms of cell counts, particularly in the glioblastoma multiforme. Thus the comparative dipeptidase activity of the gliomas does not seem to parallel their growth potential. However, it is difficult to assess the biological significance of such findings in glial tumors because of current ignorance concerning the metabolic and biochemical properties of normal neuroglia.

DR. RAYMOND D. ADAMS: I think this type of presentation can only excite our admiration. It is a fine start in a difficult problem. The material was clearly present, but its significance might be clearer, as was pointed out. What we know about brain tumors is clinical diagnosis and histological classification. I doubt if we have anything like a reasonable theory as to their cause, and those of us who work with them from day to day are all too aware of the lack of satisfactory methods for treating them. Our neurosurgical colleagues struggle with them and accomplish a little at times. The majority of cases do not lend themselves very satisfactorily to a surgical approach—not from the point of view of any long-term or curative results.

It is evident from microscopic sections that the older theory that these tumors are derived from some embryonal cell or anaplastic element residing in the nervous system is probably fallacious. If the very interesting work done by Dr. Alexander and others on experimental tumors has taught anything, it is that under the proper chemical stimulus a normal glial element can be induced to undergo neoplasia. In the brains of some patients with gliomas, you can find isolated tumor cells, as if some chemical influence had acted upon an occasional cell, one or two, here and there, inducing in them a neoplastic change. The most reasonable speculation is that there is some alteration in the metabolism of the cell. No one seems to have any idea of what that is.

The microchemical approach is certainly a worth-while one. I suppose Drs. Allen and Pope would agree that they have hardly scratched the surface. I get uneasy in seeing them struggle with the histological methods of classification. In the neurocytoma the cells had processes and something that looked like neurofibrillae, but an absence of Nissl bodies. Every one of these criteria may be open to question. That tumor may have been a true glioma, thus bringing the biochemical data into line with the others. The same is true of other tumors, differentiation of astrocytomas from oligodendrogliomas being far from reliable. In a single tumor you may find different cell types. You are trying to make a biochemical assay of something impure from the histological point of view, but the best thing is to continue the work and not stop at this point just because the first results do not seem to have revealed anything extremely exciting. I think you may come upon a few tumors in which you can find a sample that is pure. I wonder whether it would be worth while to look for other biological criteria with which to correlate biochemical data, such as total nuclear mass or total nucleoprotein content, or even mitotic activity. It would be of interest to use other histological criteria than simply the type of cell. I feel that this study is just a beginning in an important field. If one could really find basic differences between normal and neoplastic glial cells, it might open a new field in brain tumor diagnosis and therapy.

Dr. Jordi Folch-Pi, Belmont, Mass.: A point worth emphasizing is the exceedingly high oxygen consumption shown by oligodendrogliomas. Victor and Wolf published one observation, and 18 years later Heller and Elliott reported exactly the same finding in another case.

Dr. Joseph M. Foley: Is the metabolic rate in any known studies correlated with the period of time at which myelin is being laid down?

Dr. Norman Allen, Belmont, Mass.: In regard to Dr. Adams' question: The problem of histological classification is a difficult one, and one that is troublesome. I think the best we can do is to try to decide what type or types of cell are present in each specimen studied. The neurocytoma we showed was a mixture. Some parts seemed to be a neoplastic glia, whereas other islands had characteristics that suggested neurocytoma. By a lucky shot, we hit an island where the cells seemed to be solely neurocytes. In regard to nuclear mass, we haven't been able to make any correlations with cell division. In the oligodendroglioma there were not many mitoses in spite of the active oxidase levels. It is not surprising that such correlations were not possible with the particular enzymes under study, since they are present in cytoplasm rather than nucleus. We are, however, hoping to obtain satisfactory methods for microdetermination of nucleoproteins and intend to investigate this point further.

Dr. Folch mentioned and made the interesting point that oxygen consumption in oligodendrogliomas seems to be excessive, far more than what one would expect from the cytochrome oxidase activity. This and other considerations lead to the speculation that there may possibly exist in white matter and in oligodendrogliomas oxidative pathways involving enzymes other than the cytochrome system.

As to Dr. Foley's question: We have not been able to make correlations between oligodendroglia and myelin in the present study. In view of the possible relations of oligodendrocytes to the maintenance and the laying down of myelin, the possibility that the normal oligodendroglia has a higher metabolism than other glia is most interesting. One wishes to look further into this.

PHILADELPHIA NEUROLOGICAL SOCIETY

Ernest A. Spiegel, M.D., Presiding
Regular Meeting, March 2, 1956

Treatment of Trigeminal Tic (Tic Douloureux) by Injection of Gasserian Ganglion with Boiling Water. Dr. J. Rudolph Jaeger.

The injection of the Gasserian ganglion for tic douloureux is an old, well-established technique which has been used for many years. The danger in it has been recognized as due to the alcohol, which has been the customary chemical used for its destruction. The technique developed by the author employs boiling water for this purpose. It is injected by the anterior approach to the foramen ovale with the use of thiopental (Pentothal) anesthesia and x-ray guidance. The results have been similar to those after any ganglion destruction by operation or injection except that it has been singularly free of complications. There has been no facial paralysis or permanent paralysis of the muscles of mastication or extraocular nerves. In 100 cases so treated the results have been excellent and free of shock or serious complications. It seems to be a valuable substitute for the operative procedure and for the alcohol injections of the peripheral divisions in all cases of tic douloureux.

Discussion

Dr. Francis C. Grant: Dr. Jaeger has resurrected the important technique of Gasserian ganglion injections, abandoned in 1928 by most American neurosurgeons, when Dandy showed the possible devastating effects of alcohol injected into the ganglion and reaching the subarachnoid space. Dr. Cushing, in 1921-1922, was of the same opinion concerning alcohol injection into the Gasserian ganglion. Hartel developed his technique in 1914, and it was taken up particularly by Dr. Hugh Patrick, in Chicago, a year or two later. Dr. Frazier carried out a number of Gasserian ganglion injections, and I suppose that I have done 25; but, unfortunately, the technique has fallen into disuse, and I am delighted to see that Dr. Jaeger has reintroduced its use in this country. In England, Harris has used this technique in some 2000 cases, with a great degree of success. He injects alcohol.

I see no reason why Dr. Jaeger's modification of the technique and the use of boiling water rather than alcohol will not overcome most of the objections to the use of the stronger solution. If the boiling water reaches the subarachnoid space, it can probably do no great harm. Furthermore, if Dr. Jaeger's injections last for a reasonable length of time, let us say a minimum of five years, it would accomplish a great deal for these trigeminal neuralgia cases, for many of them are old and a five-year period from relief of pain may be sufficient.

We really know so little about the cause of major trigeminal neuralgia that there is no reasonable doubt that injection of boiling water should be effective.

The recent work of Taarnhøj on the decompression of the ganglion, and that of Sheldon and others, who merely stroked the ganglion with the tip of the forefinger and produced relief of pain for an appreciable period, confuse the issue still more.

Dr. Jaeger has had to reinject in only 5% of his cases, which is a satisfactorily small number. Certainly, in old debilitated patients with major trigeminal neuralgia who were unable to eat or drink because of the pain, this procedure seems to me to be very worth while. It is not perfect; no technique is, but it certainly approaches more closely to perfection than the previous use of alcohol.

Dr. Robert A. Groff: We are indebted to Dr. Jaeger for giving us another method of treatment for tic douloureux. His results are very good, although I am inclined to agree with Dr. Grant that the follow-up time is too short to permit one to evaluate the procedure entirely. It must be remembered that alcoholic injection of the Gasserian ganglion is a successful procedure, and not attended with complications frequently enough to justify discarding it. At the same time, alcoholic injection of the divisions of the fifth nerve affords a relief for as long as three or four years.

It seems as though Dr. Jaeger, by the introduction of this method, has taken a dislike to neurosurgeons by introducing a hazard. How does he handle the boiling water so as not to burn his fingers or the skin of the patient?

Dr. Jaeger states that, in making the injection, he does it under light thiopental anesthesia. The needle, when it enters the foramen ovale, pierces the third division and gives referred pain. Further introduction of the needle by 3 or 4 mm. is all that is necessary to start the injection. Is it, therefore, essential to check the position of the needle by x-ray films?

It will be very interesting to follow these patients, and I want to thank Dr. Jaeger for the privilege of discussing his paper.

DR. CHARLES RUPP: Will Dr. Jaeger tell us succinctly in what way his method is any improvement over previously available methods?

DR. MICHAEL SCOTT: This paper is a stimulating one. Dr Jaeger has shown us how one can get complete eradication of pain without too much anesthesia. Is his water technique of value in direct injection of the peripheral branches?

DR. E. A. SPIEGEL: I should like to compliment Dr. Jaeger on his very ingenious method. I am particularly interested in the use of injection of boiling water into the cerebral hemispheres and should like to inquire what the variability of lesions produced by this method is. We know from animal experiments, which go back as far as Beaunis' work, in 1868, that solutions injected into the brain substance diffuse rather irregularly. That is the reason that we injected alcohol into the pallidum in minimal amounts only and abandoned this method as early as 1950. The method has recently been rediscovered by Cooper and called "chemical pallidectomy." In the case of boiling water one is dealing, of course, only with the mechanical effect of the introduced fluid and the coagulating effect of the heat. It would be very welcome if the variability of such lesions were known. My second question concerns those cases of trigeminal pain in which the pain returns despite a total interruption of the trigeminal root. One of the mechanisms responsible for this phenomenon may be the development of hypersensitivity in the sensory nuclei in the brain stem following the elimination of afferent impulses. Experiments by Dr. M. Chavez, of Lima, Peru, carried out in my laboratory, in which the electrical activity of the external geniculate ganglion was studied following elimination of the optic impulses and that of the substantia gelatinosa trigemini after retrogasserian section of the root of the fifth nerve, seem to point in this direction. I should be much interested in hearing Dr. Jaeger's comments on which possible pathological mechanisms he considers responsible for the recurrence of pain in these cases.

DR. J. RUDOLPH JAEGER: Concerning Dr. Grant's comment in regard to the many procedures for correction of tic douloureux: There is one fundamental principle in the permanent relief of tic douloureux, and this is that the sensory root or ganglion cells must be killed or crippled for the procedure to be effective. This I have already mentioned. All of the surgical procedures which actually control the pain in some way or other affect the vitality of the ganglion cells. If they are killed, which is probable in most of these various procedures, the effect as regards the single neural element is certain to be permanent. This is the basis for injection of the ganglion with alcohol or with hot water. This has been proved by many procedures which destroy nerve cells and by use of electrocoagulation of the medial meningeal artery and other vessels near the ganglion. My results, as shown, demonstrate the fact which is well known, namely, that destruction of the ganglion cells by any method causes a permanent cure when the cells that have been killed are the ones that have caused the pain. A 5% failure in relieving tic douloureux is extremely small by any method, and it is to be remembered that should the pain extend to unanesthetized portions of the fifth cranial nerve, this pain can be relieved as easily as the initial pain at a subsequent injection. Actually, the failures in my series have been in the very early cases, from a lack of skill in using the technique. The amount of water needed, as asked of me, is not more than 2 cc. at a time. The x-ray merely gives additional security in the precise location of the injection. By using this, even though the procedure is slightly prolonged, one can be extremely accurate in the injection. The question of why water is used instead of alcohol would seem to be obvious, since alcohol leaves a watery solution of the alcohol when it enters the cerebrospinal fluid. Hot water does not affect the peripheral nerve trunks as readily as when the ganglion cells are injected with it.

Dr. Spiegel asks about the extent of the lesions produced when hot water is injected into the brain. I have used water at 75 C for performing lobotomy in 45 cases. Water at this temperature in 2.5 to 3 cc. amount, which is the maximum I have felt to be safe, will cause a lobotomy effect without evidence of gross necrosis of brain tissue. Punctate lesions can be produced by using smaller amounts of water, but these will probably not be of a gross destructive type.

Evaluation of Mestinon in Treatment of Myasthenia Gravis. Dr. Nathan S. Schlezinger.

The evaluation of Mestinon (pyridostigmine) bromide is based upon a survey of 35 patients observed in the myasthenia gravis clinic of the Jefferson Hospital. It is concluded that, in comparison with neostigmine, the vast majority of myasthenic patients have obtained a distinctly greater benefit with Mestinon. There is usually a more sustained level of response, as well as a reduction in the frequency of administration. Particularly helpful in some patients has been the elimination of the need for medication at night. Another advantage with Mestinon therapy has been the considerably reduced incidence of toxic manifestations as compared with that for neostigmine. It is not evident in this group that cranial nerve musculature is benefited more than the skeletal musculature of the body, as has been reported by other observers. The treatment of choice for most patients with myasthenia gravis would now appear to be combined Mestinon and ephedrine medication.

Discussion

Dr. Charles Rupp: My experience with Mestinon has been quite limited. I have used it in a few cases in which toxic manifestations developed with fairly large doses of neostigmine. I attempted to substitute Mestinon along with a reduced neostigmine dosage, and the patients complained even more severely of toxic manifestations, so that it was necessary to stop the Mestinon. I wonder if Dr. Schlezinger has had any similar experiences?

Dr. Nathan S. Schlezinger: I appreciate the discussion. Most observers have too limited an experience with Mestinon. I should like to ask Dr. Rupp whether his patients were on large doses of neostigmine before they were changed to large doses of Mestinon? Patients who are refractory to treatment show toxic effects from any of these drugs used in large doses. Mestinon has very definite advantages over neostigmine for most myasthenic patients, the effect of Mestinon being relatively more sustained. However, one of my patients preferred neostigmine to Mestinon; she stated that she got a more rapid and more pronounced boost from neostigmine. Since neostigmine and Mestinon are closely related chemically, they can be freely substituted for each other.

Subarachnoid Hemorrhage Associated with Subacute Bacterial Endocarditis. Dr. Homer Ray (by invitation) and Dr. K. Wahal (by invitation).

Four cases were presented in which subarachnoid bleeding occurred during the course of subacute bacterial endocarditis. In two cases the hemorrhage resulted from rupture of a true mycotic aneurysm. Infected clots were demonstrated in a branch of the middle cerebral artery, resulting in focal acute arteritis and necrosis of the vessel wall. In the third case, a typical narrow-necked saccular or berry aneurysm was found at the bifurcation of the middle cerebral artery in the Sylvian fissure, with necrosis of the fundus and neutrophilic infiltration of this portion of the sac and the adjacent brain tissue. The fourth case had a large congenital aneurysm at the bifurcation of the basilar artery. The entire sac was necrotic and infiltrated with neutrophiles. In addition, one posterior cerebral artery contained a partially organized, infected clot, which had caused focal acute arteritis. It was concluded that subarachnoid bleeding associated with subacute bacterial endocarditis is not necessarily due to rupture of a mycotic aneurysm. However, in the two cases in which a berry or congenital aneurysm was demonstrated, the presence of infection was an important factor in the rupture of the aneurysm.

Discussion

Dr. Helena E. Riggs: We have studied 175 cases of subarachnoid hemorrhage due to rupture of an aneurysm of the circle of Willis. In five instances subacute bacterial endo-

carditis was present. In structure and location the aneurysms in these five cases were similar to those in all the other cases. In the two reported in this paper an acute inflammatory process had occurred in the wall of a congenital sac.

In our experience a mycotic aneurysm of the cerebral vessels is microscopic in size. The mere infiltration of leucocytes into the coats of a berry aneurysm is no proof of mycotic origin. This reaction can be found in many of the congenital aneurysms when slow leakage precedes rupture or the patient survives for several days. In comparison with the massive bleeding usually associated with rupture of a congenital aneurysm, hemorrhage from mycotic aneurysms, in our experience, is either localized or limited to the subarachnoid space over the vertex and convexity.

DR. NATHAN S. SCHLEZINGER: I would like to ask the authors whether in any of their four cases there was the usual dramatic onset associated with spontaneous subarachnoid hemorrhage. Was the subacute bacterial endocarditis known before the onset of hemorrhage?

DR. HOMER RAY: Subacute bacterial endocarditis was known before death in all cases. In our fourth case, the patient had had a previous cerebral vascular accident, but there was no evidence of subacute bacterial endocarditis at that time.

Section on PSYCHIATRY

The Time Sense

Estimation of One Second Durations by Schizophrenic Patients

WILLIAM T. LHAMON, M.D.
and
SANFORD GOLDSTONE, Ph.D., Houston, Texas

Introduction

Variations in the estimation and judgment of time passage, in the reproduction of intervals, and in the subjective attitude to the flow of time occur in many psychopathological states and in the healthy person from time to time. Schilder [8] has reviewed the psychopathology of time and noted that the schizophrenic patient may have a disturbance in the subjective feeling of time but not in the perception of time. Aubrey Lewis [5] noted that alteration of the consciousness of time is a primary alteration and predicted that such alteration would be found as often as it is looked for. In general, there is difficulty in studying quantitatively the estimation of time, and there is a relatively small amount of experimental work in the subject on psychiatric patients. Pieron,[7] François,[1] and Hoagland [2] developed the notion that the mechanism of time perception in the human organism depends on the rate of chemical reactions and is dependent on temperature changes. Various methods of determining the sense of time have been used; among these are tapping rates, reproduction verbally or manually, statements by the subject about durations presented visually or as sounds, and statements by the subject about the simultaneity of two presented stimuli. Experiments [9] in which the subjects indicate the source of a sound demonstrate a remarkable ability in the human to resolve small temporal intervals in the region of 50μ sec. or less, although the subject is not necessarily aware of his performance. Studies of the ability of subjects to estimate longer time intervals in the region of minutes or hours suffer from the difficulty that there are numerous clues available which cannot easily be eliminated in the experimental design.

Schizophrenic patients often make statements to the effect that "time is standing still." It was because of such observations, and because of a general interest in the time sense, that the present experiments were undertaken. In order to minimize the effect of clues, and because of the possibility of observing a cultural effect, we selected, as a point of departure, the duration of one clock second as the region to be studied. Since clinical observation of the autistic schizophrenic person suggests that he frequently tends to overestimate externally determined durations, it was predicted that a patient group would provide a concept of one second that is significantly smaller than the "private second" obtained from a comparable control group.

Received for publication July 26, 1956.

Supported in part by a grant from the National Institute of Mental Health, USPHS M-1121.

M. D. Anderson Department of Psychiatry, Baylor University College of Medicine, Texas Medical Center.

Mr. A. Weinstein and Dr. V. Eisen helped in collection of data, and the staffs of the VA Hospital, the Methodist Hospital, and the Jefferson Davis Hospital, all of Houston, gave us permission to examine patients.

Method

A modified Hunter timer[8] activated an audio oscillator that delivered through headphones a tone of approximately 725 cps for selected durations of between 0.1 and 2.0 seconds. The apparatus allowed durations to be presented in step intervals of 0.1 second. Amplitude of the sounds was comfortable and constant. The apparatus had a repeat reliability of 1% and delivered selected durations within a reliability of 5%.

Thirty-seven schizophrenic patients were tested. The mean age of the patients was 33 years; there were 34 men and 3 women. All patients were hospitalized on treatment services and, in most instances, consisted of a chronically ill population. Patients were diagnosed by the hospital staffs, and these diagnoses were accepted in the experiment. Patients consecutively available to us were used; the experimenters did not select patients except that high-school education or better was required, and the five patients who were not able to do the test were not considered.

Forty-one healthy college students were tested as control subjects. There were 31 men and 10 women, with a mean age of 27 years, in this group.

The sounds were presented to all subjects through earphones. The subject was required to report whether the duration he heard was more or less than one second. It was found that random presentation of durations gave results similar to a modified ascending-descending method; the latter method was used because of greater ease of testing. Twenty alternating runs of ascending and descending durations were provided, starting at 1.0 second. If the subject reported "more" to the initial 1.0-second stimulus, the first run descended by 0.1-second step intervals and terminated when the subject reported "less" on three consecutive occasions. The subsequent run started 0.1 second below the last of the three consecutive reports of "less" and ascended by 0.1-second step intervals until the patient or subject reported "more" on three consecutive occasions, whereupon the ascending run terminated. In the event that the patient or subject reported "less" to the original 1.0-second stimulus, the first run was of an ascending nature until three consecutive reports of "more" were given, when the run terminated, the subsequent run being of descending nature. Subjects were unaware of the length of the duration to which they responded. After 20 runs a one-minute rest was allowed. After the rest period, the subjects were provided with five consecutive one-second durations, with instructions that these durations were exactly one second long and that they were to use this information in the folowing test. Subjects were then retested immediately in a manner identical with the procedure prior to information, with 10 ascending-descending runs starting at 1.0 second.

The percentage of reports of "less" for the 10 runs prior to information and that for the 10 runs following information were plotted on normal probability paper and a straight line visually fitted. The duration at which the subject reported "more" and "less" 50% of the time, and the slope, or standard deviation, of the subject's judgments were derived from these plots. The 50% point on these tests was designated the second estimation point (SEP), or that duration which that subject at the time of the test believed to be one second of clock time.

Results

A log-normal distribution (Table 1) of second estimation points (SEP's) was found.

Table 2 shows the mean log SEP with standard deviation for the patient and control groups before and after information. In such a distribution, the log mean approximates the median. This value is also reported to provide a frame of reference. Before information the "median" SEP for the control group is 0.538 second; for the schizophrenic group, 0.308 second. The smaller mean log of the schizophrenic group differs significantly (P less than 0.005) from the mean log SEP of the control group. Thus, it is suggested that both groups tended to overestimate the duration of one clock second and that, as predicted, this tendency is more marked in the schizophrenic group. It is of interest that 42% of the control group had an SEP of 0.63 second or more, while only one patient, or 3%, of the schizophrenic group showed an SEP this large.

It will be seen that in the test period following the five 1.0-second informational durations both patients and control subjects had an increase in the "median" SEP in the direction of, but not reaching, 1.0 clock second. Healthy controls changed from 0.558 to 0.762 second with information, while the schizophrenic patients changed from 0.308 to 0.668 second. The patient group, however, was more variable after information than the control group, as indicated by the standard deviations of the log

TABLE 1.—*Data for Patients and Normal Subjects Giving Values for Sex; Age; Second Estimation Point (SEP); Intrasubject Variability, or Standard Deviation of the SEP (S.D.); Second Estimation Point After Information (SEP/Inf.), and Intrasubject Variability, or Standard Deviation of the SEP/Inf (S.D./Inf.)*

Normal Subjects							Schizophrenic Patients						
No.	Sex	Age	SEP	S. D.	SEP Inf.	S. D. Inf.	No.	Sex	Age	SEP	S. D.	SEP Inf.	S. D. Inf.
1	M	23	0.40	0.19	0.80	0.19	1	F	30	0.37	0.03	0.62	0.06
2	M	24	0.50	0.02	0.86	0.08	2	F	16	0.22	0.04		
3	M	21	0.40	0.08	0.90	0.16	3	M	30	0.20	0.02	0.60	0.02
4	M	22	0.88	0.17	0.91	0.10	4	M	28	0.35	0.10	0.59	0.10
5	M	26	0.76	0.16	0.66	0.05	5	M	32	0.39	0.32	0.78	0.15
6	M	23	0.84	0.08	0.90	0.14	6	M	23	0.61	0.09	1.11	0.27
7	M	30	0.53	0.06	0.55	0.11	7	M	35	0.30	0.02	0.21	0.02
8	M	19	0.30	0.08	0.52	0.10	8	M	25	0.46	0.04	0.76	0.12
9	M	34	0.82	0.20	0.76	0.19	9	M	33	1.85	0.26	0.65	0.11
10	F	21	0.35	0.17	0.77	0.12	10	M	21	0.49	0.08	0.76	0.13
11	F	30	0.50	0.02	0.80	0.02	11	M	29	0.29	0.10	0.50	0.16
12	F	25	0.16	0.05	0.60	0.21	12	M	33	0.30	0.08	0.36	0.08
13	F	20	0.81	0.02	0.78	0.06	13	M	37	0.20	0.02	0.32	0.14
14	M	24	0.60	0.02	0.63	0.05	14	M	27	0.22	0.02	1.78	0.19
15	M	20	1.46	0.42	1.10	0.09	15	M	45	0.35	0.04	0.58	0.02
16	M	29	0.05	0.02	0.65	0.06	16	M	28	0.20	0.15	0.50	0.12
17	M	33	1.28	0.22	1.13	0.21	17	M	26	0.15	0.00	0.71	0.17
18	M	21	0.70	0.07	0.89	0.22	18	M	33	0.21	0.02	0.76	0.12
19	M	26	0.69	0.08	0.80	0.17	19	M	31	0.45	0.08	0.95	0.18
20	M	24	0.32	0.06	0.70	0.06	20	M	41	0.39	0.15	0.73	0.12
21	M	19	0.38	0.07	0.55	0.06	21	M	37	0.52	0.16	0.46	0.11
22	M	25	0.60	0.12	0.56	0.10	22	M	45	0.27	0.02	0.93	0.27
23	M	22	0.95	0.29	0.81	0.02	23	M	30	0.37	0.14	0.51	0.02
24	M	25	0.40	0.08	0.59	0.02	24	M	40	0.39	0.02	0.68	0.07
25	M	42	0.87	0.12	0.70	0.08	25	M	38	0.19	0.08	1.24	0.22
26	M	32	0.58	0.02	0.72	0.02	26	M	21	0.37	0.02	0.42	0.06
27	M	28	0.80	0.16	1.06	0.17	27	M	25	0.15	0.00	0.5	0.02
28	M	23	0.32	0.02	0.70	0.19	28	M	25	0.61	0.13	0.59	0.07
29	M	37	0.42	0.10	0.85	0.13	29	M	37	0.63	0.08	0.89	0.36
30	M	27	0.50	0.02	0.69	0.02	30	M	30	0.38	0.16	0.36	0.09
31	F	21	0.56	0.05	0.84	0.11	31	M	34	0.29	0.02	0.82	0.08
32	M	28	0.70	0.08	0.89	0.11	32	M	37	0.31	0.02	0.41	0.02
33	M	22	2.68	0.44	0.84	0.20	33	F	23	0.10	0.02	1.45	0.27
34	F	45	0.30	0.02	1.38	0.14	34	F	38	0.22	0.06	0.73	0.26
35	F	26	0.35	0.03	0.80	0.11	35	M	44	0.10	0.02	1.68	0.68
36	F	39	0.79	0.06	0.85	0.11	36	M	37	0.19	0.02	0.88	0.16
37	F	39	0.54	0.19	0.54	0.17	37	M	24	0.44	0.11	0.77	0.09
38	F	35	0.51	0.16	0.73	0.13							
39	M	22	0.80	0.08	0.84	0.11							
40	M	26	0.56	0.16	0.80	0.22							
41	M	24	1.46	0.17	1.22	0.15							

TABLE 2.—*Mean Log Second Estimation Point (SEP), Standard Deviation of Mean Log SEP, and Antilog of Mean Log SEP for Patient and Control Groups Before and After Information*

Group	No.	Before Information			After Information		
		Mean Log SEP	S.D.	Antilog SEP	Mean Log SEP	S.D.	Antilog SEP
Control	41	$\bar{1}.7468$	0.279	0.558	$\bar{1}.8917$	0.097	0.762
Patient	37	$\bar{1}.4895$	0.240	0.308	$\bar{1}.8248$	0.197	0.668

means. This greater variability of the patient group after information reflects the tendency of this group to "undershoot" or "overshoot" the mark (one second clock time) on being tested immediately after having been given information as to the real length of a clock second. It seems apparent that the control subjects became more homogeneous as a group with respect to their estimate of one second following information about the exact length of such a duration, while the schizophrenic patients were relatively less homogeneous as a group in this respect immediately after such information. The change in mean log SEP of both groups before and after information is statistically significant (P less than 0.005).

Intrasubject variability of the control subjects and that of the patient group were similar. Mean standard deviation of judgments was 20% of the group mean second estimation point (SEP) in the case of the control subjects and 18% in the case of the patients, before information. The SEP-standard deviation ratio of individuals was fairly unchanged throughout the range oc-

cupied by the SEP in normal subjects and in patients.

Comment

These data suggest that the schizophrenic patient is likely to overestimate the duration of a clock second to a greater degree than are comparable normal controls. This finding is apparently in line with clinical observations of the inner-directed, autistic person's tendency to overestimate temporal events based upon external occurrences.

The derived SEP, or a subject's private notion of the duration of a clock second, was found to be surprisingly stable over the approximately 10 minutes required for the test procedure. The nature of variation of the SEP over hours or throughout days or weeks in a normal or a patient population is not known. We do not know whether remission in the patient group would be accompanied by a lengthened SEP. In addition to the described findings, there is preliminary evidence [6] of a variation in the personal estimate of a second with fatigue, with alteration of metabolism, with the degree of boredom, and with administration of certain pharmacologic agents.

It is clear that when one discusses experienced duration, it is important to denote the character of the operation used by the subject to mark the time. It appears to us that the "second" indicated or marked by the subject by means of counting aloud, or by tapping, or by holding down a lever for a given estimated amount of time is not the same as the passive estimation of time obtained by listening to durations, as in this series of determinations. There is evidence that the inclusion of muscular movement into the estimation affords cues which then cause the SEP to be more nearly congruent with a clock second than when there is not the use of some such muscular activity during the estimation. Preliminary studies of this point tend to bear out these conclusions, and detailed investigations to determine systematic effects, if any, of muscular cues are in progress. It may be that the schizophrenic patient's autistic separation from external events associated with his passivity prevents full utilization of sensory and motor cues in making consensually valid temporal judgments. We would expect the schizophrenic subject to make less use of remote sensory information and current kinesthetic cues in deriving his "second." In this study, we attempted to minimize anchor or frame-of-reference effects by beginning each test with a one-second stimulus. On the basis of these findings it would appear of interest to determine the differential effect of anchors (initial stimuli) far removed from one second upon the SEP measure in control and schizophrenic groups, as well as the effects of anchor sequences. The latter data would provide information relevant to a subject's utilization of more remote frames of reference in current judgments. It would also appear relevant to obtain data from schizophrenic and normal subjects counting aloud, with the hypothesis that the patient group would not achieve the increased measure of accuracy associated with kinesthetic information.

When control subjects were asked by what means they determined whether or not a stimulus was more or less than a second, most of them stated that they counted to themselves some such phrase as "one thousand and one." Inasmuch as some of the controls and patients said that they did this when their second estimation point was less than 0.3 second, the meaning of this statement is not clear. The difference between active overt use of muscles in making the estimates and the use of more passive methods is highlighted.

In general, it was our feeling in watching the patients and the controls, with particular emphasis on the normal subjects, that the more extroverted and outgoing subjects were the ones who had SEP's at the long end of the distribution, while the more introverted, retiring, and shy subjects had the shorter SEP's. The subject's feeling of certainty with respect to the accuracy of his decision was, if anything, negatively related to the accuracy of his SEP. It seemed that those subjects who felt that the test was unfair

because their occupation (navigator, horse trainer, dancer, photographer) led them to know the actual duration of a clock second were without exception persons with long SEP's of greater than one clock second. It is almost as though these trained subjects were lost without their learned cues. Since the characteristic personality of the schizophrenic patient is presumed to be turned inward, these observations are in accord with clinical observation. Sixteen of the patients were receiving varying amounts of chlorpromazine, ranging in amount from 100 to 1600 mg. daily. No significant difference between these patients and those who were not receiving the drug was found.

It is assumed that the concept of one second held with such surprising stability and tenacity by our subjects and patients is in part learned from the cultural influences surrounding each person. Preliminary studies directed to the questions of how and when the person acquires his concept of a second are underway and will be reported. None of the data so far obtained tend to show a correspondence between the child's performance on these tests of time perception and the behavior of the schizophrenic patients. Studies of the time sense of subjects from another cultural background are also underway.

While it may be possible that some factor associated with hospitalization alone is responsible for the short SEP of the schizophrenic patients, we do not believe such to be the case. A few studies on patients with chronic disease other than mental illness hospitalized for comparable lengths of time have not shown significantly short SEP's.

Summary

Thirty-seven schizophrenic patients were compared with 41 control subjects with respect to their estimation of one clock second's duration. It was found that the group of patients had a significantly smaller second estimation point (SEP) when tested by a "passive" method than did the control group. Patients and control subjects were surprisingly stable in their estimates. The effect of providing information of the actual duration of a clock second was studied in both groups. The relation of these findings to the psychopathology of schizophrenia is briefly discussed.

REFERENCES

1. François, M.: Contribution à l'étude du sens du temps, Ann. psychol. 28:186, 1928.

2. Hoagland, H.: The Physiological Control of Judgments of Duration: Evidence for a Chemical Clock, J. Gen Psychol. 9:267, 1933.

3. Hunter, J., and Brown, J.; A Decade-Type Electronic Interval-Timer, Am. J. Psychol. 62:570, 1949.

4. Klemm, O.: Über die Wirksamkeit kleinster Zeituntershiede, Arch. ges. Psychol. 50:204, 1925.

5. Lewis, A.: Experience of Time in Mental Disorder, Proc. Roy. Soc. Med. 25:611, 1932.

6. Lhamon, W.: Time and Rhythm in Psychosomatic Relationships, in Current Problems in Psychiatric Diagnosis, edited by P. Hoch and J. Zubin, New York, Grune & Stratton, Inc., 1953, Chap. 16.

7. Piéron, H.: The Sensations: Their Functions, Processes and Mechanisms, translated by M. H. Pirenne and B. C. Abbott, New Haven, Conn., Yale University Press, 1952.

8. Schilder, P.: Mind: Perception and Thought in Their Constructive Aspects, New York, Columbia University Press, 1942.

9. Wittmann, J.: Beiträge zur Analyse des Hörens bei dichotischer Reizaufnahme, Arch. ges. Psychol. 51:21, 1925.

Glutathione Levels in Mental and Physical Illness

STEN MARTENS, M.D.
BYRON E. LEACH, Ph.D.
ROBERT G. HEATH, M.D.
and
MATTHEW COHEN, New Orleans

Several authors * have reported lower levels of reduced glutathione (GSH) in the blood of patients with endogenous psychosis. Recently, in our search for possible biochemical correlates of schizophrenia, we found evidence that these patients oxidized adrenaline more rapidly than normal persons without systemic disease.† Our data indicated that the increased speed of adrenaline breakdown was not specific for schizophrenia, and we therefore have been searching for a more basic substance which might shed light on this observation. Since lower glutathione levels seem to be a quite consistent finding, we were interested in exploring this phenomenon further to determine if it might be related to our findings with adrenaline metabolism. In the present study, we have compared the glutathione levels of hospitalized schizophrenic patients and outpatient, so-called "pseudoneurotic," schizophrenics with levels obtained from normals and patients without evidence of psychosis, but with a variety of systemic diseases. We compared these findings with the results we obtained in similar subjects with the adrenaline oxidation test. Since the results on the two tests were in some ways comparable, we have conducted other studies,[10] which indicate that ceruloplasmin, a known oxidizing enzyme and/or a closely related enzyme, may possibly play a role in both phenomena, i. e., in the increased speed of adrenaline oxidation and in the lowering of levels of reduced glutathione.

Received for publication July 2, 1956.

From the Department of Psychiatry and Neurology, Tulane University School of Medicine. Special Foreign Fellow, The Commonwealth Fund (Dr. Martens). Supported by grant-in-aid from The Commonwealth Fund.

* References 1, 2.

† References 3, 4.

Method and Materials

Method.—The method employed in this study is based upon the color reaction between sodium nitroferricyanide (nitroprusside) and GSH, as described by Grunert and Phillips.[5] It is briefly summarized as follows:

One-half milliliter of venous blood is hemolyzed in distilled water and saponin and thereafter immediately precipitated with 3.0% metaphosphoric acid. After saturation with NaCl, the sample is centrifuged at 2500 rpm for 10 minutes and filtered. A 2 ml. aliquot of the filtrate is pipetted into 6 ml. of saturated NaCl solution. To obtain a reasonably stable color reaction (two minutes), 1 ml. of 0.067 M sodium cyanide in 1.5 M sodium carbonate solution is added before 1 ml. of sodium nitroferricyanide. The sample is read in a Beckman DU spectrophotometer at 520 mμ against a blank containing saturated NaCl solution, 2.0% metaphosphoric acid, and the same color reagent. Fresh standards are prepared every day, since there is a definite, although minimal, auto-oxidation in the GSH standard within 24 hours. The obtained sample concentrations are calculated against the hematocrit values, and the final value thus obtained is expressed in milligrams of GSH per 100 ml. of red blood cells. This is called the glutathione index (Altschule). Before the final study was begun, several recovery tests were done in which 90.0% of an added standard of known concentration was recovered from the samples.

Material.—In each patient in a group of 20 hospitalized chronic schizophrenics, three subsequent determinations were made at one- to three-day intervals. These patients were all men, 32 to 66 years of age. The duration of their illness varied from 2 to 30 years, and they had been hospitalized between 2 and 30 years. At the time of the study none of them had had any physical treatment for at least two weeks. Each determination was made

in duplicate from which the average optical-density value was calculated. The average value of the three determinations thus obtained was calculated, and the means of these averages were analyzed statistically.

The control group consisted of 22 normal subjects, all employees of the Department or members of the staff and known to be free from psychotic symptoms or systemic disease. Two to three determinations, all in duplicate, were made at one- to seven-day intervals. The average GSH indexes were calculated and analyzed statistically.

The third group consisted of 20 pseudoneurotic schizophrenic outpatients. In each patient, one to two determinations, in duplicate, were made, as in the other groups, and the average values analyzed in the same way.

A fourth, so-called "nonspecific" (the term was adopted because they did not have schizophrenia), group consisted of 23 subjects. Of this group, 6 had acute respiratory illness or were in convalescence after such illness; 17 suffered from chronic pulmonary tuberculosis but had no history of psychosis, and 2 had chronic neurologic disease. In this group, one to two determinations, all in duplicate, were made and the values analyzed statistically. In studying this group, it was found that patients with high sedimentation rates tended to have low GSH indexes. An exception was encountered, however, in tuberculosis patients under active treatment. Patients with tuberculosis under treatment with PAS, streptomycin, and isoniazid showed comparatively high indexes, in spite of their often exceedingly high sedimentation rates. The material was therefore extended to include a fifth group, comprised of four untreated tuberculosis patients with high serum globulin and six patients with high serum globulins in association with other diseases. This group was designated "nonspecific-U" (indicating untreated), whereas the first "nonspecific" group was designated "nonspecific-T" (indicating patients under treatment).

In all studies, if the difference in optical density between the two duplicates exceeded 15 units, the determination was not used.

Results

The data are tabulated according to groups. Schizophrenic patients with normal serum globulin levels and patients without psychotic behavior, but with elevated levels of serum globulin, showed significantly lower levels of reduced glutathione than the group of normal subjects and the patients under treatment for active tuberculosis. In our Tables we use the term "nonspecific"

TABLE 1.—*Glutathione (GSH) Indexes in Chronic Schizophrenic Patients*

Patient	No. of Determinations	GSH Index Average	GSH Index Range
1	3	65	12
2	3	64	21
3	3	62	10
4	3	66	7
5	3	65	9
6	3	68	6
7	3	62	8
8	3	57	17
9	3	68	7
10	3	71	12
11	3	62	5
12	3	70	18
13	3	67	30
14	3	65	8
15	3	62	6
16	3	69	32
17	3	68	47
18	3	62	39
19	3	62	34
20	3	65	17
Total: 20	Total: 60	Mean: 65±3.5	6-47 Over-all range

TABLE 2.—*Glutathione (GSH) Indexes in Controls*

Patient	No. of Determinations	GSH Index Average	GSH Index Range
1	2	81	19
2	2	73	17
3	2	84	0
4	2	85	9
5	2	85	22
6	3	78	14
7	3	83	6
8	3	81	30
9	2	73	13
10	2	58	5
11	2	82	25
12	2	66	6
13	2	87	1
14	2	81	13
15	2	78	14
16	2	80	13
17	2	69	23
18	2	80	2
19	2	78	4
20	2	69	8
21	2	77	9
22	2	77	17
Total: 22	Total: 47	Mean: 78± 7	0-30 Over-all range

TABLE 3.—*Glutathione (GSH) Indexes in Pseudoneurotic Schizophrenics*

Patient	No. of Determinations	GSH Index Average	GSH Index Range
1	2	58	12
2	2	88	3
3	1	61	
4	1	57	
5	2	87	11
6	1	65	
7	1	63	
8	1	92	
9	1	73	
10	1	82	
11	1	82	
12	1	52	
13	1	70	
14	1	64	
15	1	62	
16	1	64	
17	1	70	
18	1	73	
19	1	60	
20	1	60	
Total: 20	Total: 26	Mean: 69±11.2	3-12 Over-all range

TABLE 4.—*Glutathione (GSH) Indexes in Nonpsychotic Patients with Somatic Diseases (Nonspecific-T)*

Patient	No. of Determinations	GSH Index Average	GSH Index Range
1	2	60	4
2	1	72	
3	1	64	
4	1	82	
5	1	74	
6	1	57	
7	1	82	
8	1	92	
9	1	89	
10	1	104	
11	1	89	
12	1	70	
13	1	76	
14	1	77	
15	1	77	
16	2	79	27
17	2	86	22
18	2	83	2
19	2	71	7
20	1	85	
21	1	62	
22	1	52	
23	1	76	
Total: 23	Total: 28	Mean: 77±3.7	2-27 Over-all range

TABLE 5.—*Glutathione (GSH) Indexes in Nonpsychotic Patients with High Serum Globulins (Nonspecific-U)*

Patient	No. of Determinations	Average GSH Index
1	1	68
2	1	80
3	1	65
4	1	70
5	1	65
6	1	72
7	1	58
8	1	55
9	1	58
10	1	84
Total: 10	Total: 10	Mean: 68±8.9

for patients with various somatic illnesses who did not present psychotic symptoms.

The GSH indexes obtained in the chronic schizophrenic group are seen in Table 1. The mean index in this group was 65 mg. per 100 ml. of red blood cells, with a standard deviation of 3.5. In the nonpsychotic, noninfectious control group (Table 2) the mean index was found to be 78 mg. per 100 ml. of red cells, with a standard deviation of 7. The pseudoneurotic schizophrenics showed a mean GSH index of 69 mg. per 100 ml. of red cells, with a standard deviation of 11 (Table 3). The mean index of the so-called "nonspecific-T" group was 77 mg. per 100 ml. of red cells, and the standard deviation, 3.2 (Table 4). In the fifth group, "nonspecific-U," the mean GSH index was 68 mg. per 100 ml. of red blood cells and the standard deviation 8.9 (Table 5).

As seen from the Tables, in some subjects there was considerable variation in the GSH indexes of the different determinations. This variation was, on the average, 12 in the control group, 17 in the schizophrenic group, 12 in the "nonspecific-T" group, and 9 in the pseudoneurotic group.

Comment

By analyzing these figures statistically, one finds that the GSH index in the chronic schizophrenic group is significantly lower than in the control group (at the 1% level). The index of the pseudoneurotic group shows differences both from that of the control group and from that of the chronic schizophrenic group, being, however, closer to the value for the schizophrenic group. It is slightly higher than in the latter but significantly (at the 1% level) lower than in the former group.

The "nonspecific-T" group, however, shows practically no difference in GSH index as compared with the normal. As compared with that for the chronic schizophrenic group, however, the value is significantly (at the 1% level) higher. In the "nonspecific-U" group, which contains the patients with elevated serum globulins, including patients with untreated tuberculosis and patients with liver disease and chronic neurologic disease, one finds significantly (at the 1% level) lower GSH indexes than in the healthy controls and the "nonspecific-T" group.

The mean GSH indexes found in this study are higher in all groups studied than those reported by Altschule and co-workers. The probable explanation is that different methods were used. Altschule and coworkers reported no recovery tests, and it therefore cannot be established exactly where the source of difference should be sought. The recovery tests in this study gave approximately 90.0% of the added quantity of GSH, thus indicating that values obtained in this study are slightly lower than actual values.

Watson and co-workers,[6] who studied GSH levels in normals and in rheumatic patients, using the color reaction method, report normal indexes of the same magnitude as we obtained. It was pointed out by Grunert and Phillips, in describing their method, that GSH rapidly oxidizes unless in acid solution, and it is thus of great importance to add, as soon as possible, the 3.0% metaphosphoric acid to the samples. In the present study the metaphosphoric acid used for precipitation has therefore consistently been added within one to three minutes after complete hemolysis has taken place.

The study of the chronic schizophrenic group as compared with the controls confirms the findings of previous investigators that the GSH index in chronic schizophrenics is lowered. It is of interest to note also that the GSH index in the group of pseudoneurotic schizophrenics is almost as low as in the chronic schizophrenics. This finding suggests that the same metabolic abnormalities may be present in schizophrenic patients even when classical secondary psychotic symptoms are not present.

In many ways the results obtained with the glutathione test were similar to those obtained on the adrenaline oxidation test by Leach and Heath.[4] However, there were also differences in results with some groups of patients. In the "nonspecific-U" (i. e., nonpsychotic) group of patients with high globulins, the changes paralleled those seen in schizophrenic patients without the high globulin levels; i. e., reduced glutathione levels were lower, indicating increased oxidation when adrenaline oxidation was faster. However, with patients falling into the "nonspecific-T" group of this study, the adrenaline oxidation test was elevated as it was in the schizophrenics, whereas glutathione levels were in the same range as is the normal group. This could be due to many factors, such as a difference in sensitivity between the two tests, or it may indicate that they are not reflections of the same basic metabolic disturbance.

Several studies suggest a relationship between the metabolism of glutathione and that of adrenaline. Randall[7] has observed that one metabolite of adrenaline, adrenochrome, interferes with the anaerobic glycolysis in rat brain, and that GSH prevents this inhibition. Walaas and Walaas[8] recently presented further evidence to suggest the nature of the relationship between glutathione and adrenaline metabolism. They showed that adrenochrome interferes with the glycolysis in vitro by inhibiting hexokinase. Their studies demonstrated that GSH, a known activator of sulfhydryl enzymes, plays a role in adrenaline oxidation, possibly by counteracting the effects of certain adrenaline metabolites. In an earlier study,[4] we reported that the presence of copper ions increased the speed of adrenaline oxidation, whereas cyanide inhibits the reaction. This fact, plus the information[9] that ceruloplasmin, a copper-containing globulin in serum, is an oxidizing agent, led us to conduct studies to determine whether the presence of the oxidizing enzyme, ceruloplasmin, might be playing a responsible role in affecting both the GSH levels and the adrenaline metabolism. Studies which we have conducted with ceruloplasmin indicate that this enzyme rapidly oxidizes free glutathione in vitro and that the oxidation is inhibited by cyanide. This lends support to the above-mentioned findings by other investigators. We have also conducted extensive studies which indicate that ceruloplasmin and/or a closely related substance is the principal oxidizing enzyme for adrenaline found in human serum. This study is the subject of a separate report.[10]

Summary

Our findings of lower levels of reduced GSH in schizophrenics than in normals confirm reports of other workers. This finding is not specific for schizophrenic patients, since we find it also in patients with various intercurrent diseases. There appears to be a relationship between lower GSH levels and high levels of serum globulin. These results are compared with those

which we reported earlier regarding the speed of adrenaline oxidation. In that study, many patients without psychosis, but with other disease processes, similarly showed changes characteristically seen in psychotics. In some instances, however, where adrenaline metabolism was altered, the GSH levels were in the normal range. The question whether the same enzymatic system may affect both indicators, or whether they are more indirectly related to each other, is discussed. Further explorations of the role of ceruloplasmin and/or closely related substances in association with these biochemical abnormalities are presented in a separate paper.[10]

REFERENCES

1. Ljungberg, E.: Some Observations on Behavior of Blood Glutathione, Particularly During Insulin Shock Treatment, Acta psychiat. et neurol. scandinav. (Supp.) 47:172, 1947.

2. Altschule, M. D.; Siegel, E. P., and Henneman, D. H.: Blood Glutathione Levels in Mental Diseases Before and After Treatment, A. M. A. Arch. Neurol. & Psychiat. 67:64, 1952.

3. Heath, R. G., and Leach, B. E.: Multidisciplinary Research in Psychiatry, in Changing Concepts of Psychoanalytic Medicine, edited by Sandor Rado and George E. Daniels, New York, Grune & Stratton, Inc., 1956, pp. 201-224.

4. Leach, B. E., and Heath, R. G.: The in Vitro Oxidation of Epinephrine in Plasma, A. M. A. Arch. Neurol. & Psychiat. 76:444, 1956.

5. Grunert, R. R., and Phillips, P. H.: A Modification of the Nitroprusside Method of Analysis for Glutathione, Arch. Biochem. 30:217, 1951.

6. Watson, D.; Bidmead, D. S., and Kersley, G. D.: Glutathione Levels in Rheumatoid Arthritis, Arch. Rheumat. Dis. 11:292, 1952.

7. Randall, L. O.: The Inhibition of the Anaerobic Glycolysis of Rat Brain by Adrenochrome, J. Biol. Chem. 165:733, 1946.

8. Walaas, E., and Walaas, O.: Noradrenaline and Adrenochrome in Carbohydrate Metabolism, Biochem. et biophys. acta 20:77, 1956.

9. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1955, pp. 1468-1469.

10. Leach, B. E.; Cohen, M.; Heath, R. G., and Martens, S.: Studies of the Role of Ceruloplasmin and Albumin in Adrenaline Metabolism, A. M. A. Arch. Neurol. & Psychiat., this issue, p. 635.

Studies of the Role of Ceruloplasmin and Albumin in Adrenaline Metabolism

BYRON E. LEACH, Ph.D.
MATTHEW COHEN
ROBERT G. HEATH, M.D.
and
STEN MARTENS, M.D., New Orleans

For some time we have been attempting to determine whether there were biochemical alterations in schizophrenic patients which would correlate with the behavioral deviations and the physiological characteristics of this disease which we have previously reported.* There are many reports in the literature of minor and inconsistent biochemical differences between normals and schizophrenics.[3] We have reported from this laboratory alterations in the speed of adrenaline oxidation in schizophrenics † and lowered levels of glutathione[6] in association with the psychotic behavior. In our studies, however, findings on both of these tests were nonspecific in that they occurred in association with other diseases not characterized by psychotic behavior. An important consideration is the fact that other disease processes were not present in the schizophrenics who showed these changes. It seemed plausible to us, however, that the changes in these two indicators could be caused by quantitative or qualitative differences in a specific enzyme system. Several observations in regard to the adrenaline oxidation test led us to suspect the possibility that ceruloplasmin, a known oxidase, might play an important role or might be the fundamental substance in producing the increased speed of adrenaline oxidation on our test. One observation was that in disease processes other than schizophrenia in which we had found the speed of adrenaline oxidation increased, others had reported increased quantities of ceruloplasmin.‡ As one procedure in our search for the important factor in increased oxidation of adrenaline, we dialyzed the serum for 12 hours against tap water. The serum still possessed the same ability to oxidize the adrenaline in vitro, suggesting that the important substance was a large molecule, possibly a protein. These observations, coupled with reports[9] that the copper oxidized glutathione, cysteine, and ascorbic acid and would activate glycolysis (even though oxidation of adrenaline was not reported) led us to conduct studies to determine whether this enzyme might be important in producing the biochemical changes which we have noted in schizophrenic patients. We were interested in determining whether the quantitative levels of this enzyme, or perhaps more than one enzyme, might be altered in schizophrenic patients or whether they might even be qualitatively different. The data to be presented here indicate that the speed of adrenaline oxidation by serum in vitro is proportionate to the amount of copper globulin present. In studies to be reported elsewhere,§ we determined that the so-called ceruloplasmin, as extracted by the method to be described below, is qualitatively different in schizophrenics than in normals. The difference

Received for publication July 3, 1956.
Supported by grant-in-aid from The Commonwealth Fund.
Special Foreign Fellow, The Commonwealth Fund (Dr. Martens).
From the Department of Psychiatry and Neurology, Tulane University School of Medicine.

* References 1, 2.
† References 4, 5.
‡ References 7, 8.
§ Leach, B. E.; Heath, R. G.; Cohen, M., and Martens, S.: Taraxein: Method of Extraction from Serum of Schizophrenic Patients and Identification Studies, in preparation.

is that the product obtained from schizophrenics contains an additional substance which may also be an oxidase. For the purpose of the thesis to be developed in this presentation, we feel it will be less confusing if we do not consider this factor, i. e., the qualitative difference. For clarity, therefore, in developing the principal thesis of this presentation, namely, identification of oxidizing and inhibiting substances of adrenaline on an in vitro test, we shall call the substance as extracted by the method used herein ceruloplasmin. It must be borne in mind, however, that schizophrenic ceruloplasmin (i. e., as the term is to be used here) differs from that of the normal in that it contains a qualitatively different substance which apparently is also an oxidase. Our studies indicated that isolated ceruloplasmin and/or related substances oxidize adrenaline in vitro many times faster than serum containing an equivalent amount of ceruloplasmin, and also that auto-oxidation of adrenaline is faster than when adrenaline is mixed with serum. This suggested the presence of a substance in the serum which inhibited oxidation. This was also identified.

In a separate paper,[6] we have presented evidence indicating that alterations of levels in reduced glutathione in association with schizophrenia may also be influenced by the amount of copper globulin present.

Material and Methods

In this section we shall describe procedures for isolating the substances which affect our in vitro oxidation tests. These are the oxidizing substance, principally ceruloplasmin, and the inhibiting substance, which is principally albumin. Methods which we used for testing the oxidative function will be briefly described.

Extraction of Ceruloplasmin

Ceruloplasmin was prepared from the serum according to the method described by Holmberg and Laurell.[10] The procedure to be described involves the use of 10 ml. of serum. Thirty milliliters of fasting blood is drawn from the antecubital vein and allowed to clot. The serum is then cooled to 4 C, after which the globulin fraction is precipitated out by the addition of a solution of saturated ammonium sulfate equal to the amount of serum and centrifugation at 3000 rpm for two hours at 4 C. The albumin fraction is separated, and the precipitate containing the globulins is redissolved in 10 ml. of water. This solution is then dialyzed against water, which in our laboratories is consistently at a pH of between 9 and 10, for 40 hours to remove the ammonium sulfate. The euglobulin fraction is then separated by adjusting the pH to 6.2 and centrifugation. Ceruloplasmin and other globulins are next separated from this supernatant fluid by centrifugation, after first adjusting the pH to 5.5, cooling the solution to 0 C, and adding sufficient alcohol at 0 C to make the solution 12%. The precipitate, which is ceruloplasmin and other globulins, is then dissolved in water and dialyzed against tap water at the pH of 9 to 10 for 18 hours. The pH of the dialysate is then adjusted to 6.5, and the solution is cooled to 0 C and mixed with an equal volume of 90% alcohol-chloroform mixture (9:1), which also was first cooled to 0 C. This mixture is allowed to sit until it reaches 20 C, after which the precipitated and denatured proteins are separated by centrifugation. Ceruloplasmin is extracted from this precipitate by repeated extractions with saline, using 1.0 ml. of saline for the first extraction and 0.5 ml. of saline for each of the next four extractions. These extracts of ceruloplasmin are then combined and dialyzed against cold tap water overnight. The dialysate is made up to exactly 10.0 ml. in total volume. Since this is the ceruloplasmin removed from 10.0 ml. of serum, it was our assumption that we should obtain as much adrenaline oxidation from 1.0 ml. of this solution as we obtained from 1.0 ml. of human serum if ceruloplasmin (plus perhaps other products which we obtained through this extraction procedure) was the essential oxidizing substance.

In determining the quantity of copper in ceruloplasmin present in serum, we employed the formula outlined by Holmberg and Laurell.[10] Since the copper in ceruloplasmin is tightly bound by the prosthetic group of the molecule and exhibits a characteristic peak at 605 mμ, it became possible to obtain a quantitative estimate by determining the optical density. Multiplication of the optical-density reading by 5 gives the micrograms of copper present in the ceruloplasmin of 100 ml. of serum. This is virtually the total amount of copper in this quantity of serum, since 96% of copper in serum is in the ceruloplasmin fraction.[10] Quantitative values of the copper in ceruloplasmin in the sample of each test subject, as determined by this method, are presented ("Results").

Extraction of Albumin

It seemed plausible that, in addition to there being an oxidizing enzyme in the serum, there possibly or probably were also inhibitors present. Indeed, auto-oxidation of adrenaline at pH of 7.4 is greater than that found in any serum or plasma.

Experiments with the ceruloplasmin supported this assumption, since it oxidized adrenaline with much greater rapidity alone than when mixed with serum ("Results"). In early experiments we added several substances to serum to determine the manner in which they affected the speed of adrenaline oxidation and found that some substances clearly inhibited the oxidation reaction. Cyanide had this effect, as did egg albumen. Since albumin was an endogenous product in the serum, we felt that it was at least one of the factors responsible for inhibiting the oxidation reaction. It was apparent that if we were to conduct a meaningful test to determine whether or not it was the ceruloplasmin in serum that produced the oxidation of adrenaline, it would be necessary, when testing the ceruloplasmin from a given amount of serum, to add also the inhibitor from this amount of serum to the solution. A series of experiments which we conducted suggested that albumin was the prime inhibitor in the serum. The data to be presented under "Results" strongly support this contention.

The method for extracting albumin from the serum is as follows: Albumin is extracted from each sample of serum (i. e., 10 ml.) employed in the procedure for isolating ceruloplasmin by dialyzing the supernatant fluid (i. e., that part which is separated in extracting the ceruloplasmin) after the globulins were precipitated with an equal amount of saturated ammonium sulfate. The dialysate (i. e., the albumin) is then freeze-dried, and one-half of it is dissolved in 5 ml. of water. Sufficient NaCl is then added to make an 0.85% sodium chloride solution. This is the test sample labeled "albumin only."

Method for Preparation of Serum Minus Ceruloplasmin

As another test procedure to determine more precisely the exact nature of the oxidizing and inhibiting substances in the in vitro oxidation of adrenaline, we conducted tests with serum from which the ceruloplasmin had been removed. Our reasoning was that if albumin was the principal inhibitor of adrenaline in our oxidation test, then the results should be the same whether a reconstituted albumin solution or serum minus ceruloplasmin was substituted for the whole serum.

The precipitate, formed after the addition of an equal volume of saturated ammonium sulfate solution (i. e., the globulin fraction, in contrast to the supernatant albumin fraction referred to above) is dissolved in water and dialyzed. It is then precipitated with a solution of ammonium sulfate at 33% of saturation. This is centrifuged, and the precipitate is called the globulin fraction minus ceruloplasmin. Ceruloplasmin remains in the supernatant fluid at this stage in this process. The precipitate, after being dissolved in water, is dialyzed and freeze-dried. This substance then contains serum minus albumin and minus ceruloplasmin. As the final stage in preparing this serum without ceruloplasmin, the albumin extracted from the amount of serum utilized must be added and the volume of the fluid restored to the original amount of serum by the addition of isotonic saline.

Method for Preparation of Test Solution Containing Ceruloplasmin, Albumin, and Globulin

To reconstitute a solution containing all those fractions which are felt to be of importance in determining the speed of adrenaline oxidation on the oxidation test, the ceruloplasmin from the same amount of serum was added to the fraction labeled "serum minus ceruloplasmin." Theoretically this should contain all of the important factors, and, therefore, curves obtained with this preparation should be similar to those obtained with an equal amount of whole serum.

Method for Measuring Adrenaline Oxidation

The method for measuring the speed of adrenaline oxidation in vitro has been described by Leach and Heath.[5] In this procedure 1.0 ml. of serum, and in this instance the various fractions obtained from 1.0 ml. of serum and reconstituted to 1.0 ml. with saline, are mixed with 1.0 ml. of adrenaline (2 mg.) plus 1.0 ml. of 0.5 M phosphate buffer (pH 7.4) and run against a blank prepared with the same constituents, but without adrenaline, on the DK spectrophotometer. In our original reports we measured the optical-density difference at 395 mμ between a curve run at 80 minutes and a curve run at 1 minute, and the difference in optical density was used as the expression of the amount of oxidation. For greater convenience in the present experiments, the optical-density difference at 395 mμ between the curves at 60 minutes and the curves at 1 minute was used as the indicator of the amount of oxidation. The 395-mμ point on the curve was used because it was here that the maximal optical-density difference appeared on this determination.

Results

The data are presented in two tables. Sample curves from the Beckman DK spectrophotometer are reproduced in Figures 1 and 2. Table 1 shows the results with 11 nonschizophrenic controls who were well known to our staff. All results are expressed as optical density differences between the 60-minute curve and the initial curve on the DK spectrophotometer. Column 1 shows the results obtained on the various subjects by

TABLE 1.—*In Vitro Oxidation of Adrenaline*: Controls*

Control No.	Optical-Density Differences Between the 60-Minute Curve and the Initial Curve				Amount of Cu in Ceruloplasmin Fraction, γ/100 Ml. Serum
	Using Whole Serum	Using Serum Minus Ceruloplasmin	Using Albumin Only	Using Ceruloplasmin plus Albumin and Globulin	
1	0.087	0.031	0.034	0.089	95
2	0.088	0.013	0.012	0.092	95
3	0.088	0.025	0.011	0.091	98
4	0.087	0.037	0.026	0.090	100
5	0.089	0.018	0.026	0.091	100
6	0.090	0.022	0.020	0.093	110
7	0.095	0.034	0.011	0.097	125
8	0.105	0.018	0.012	0.105	140
9	0.110	0.011	0.000	0.113	147
10	0.130	0.020	0.017	0.134	164
11	0.138	0.012	0.012	0.139	170
Averages	0.101	0.021	0.016	0.104	122

* In each instance 1.0 ml. of solution is employed against 1.0 ml. of adrenaline (2 mg/ml.). For explanation of Table, see "Results."

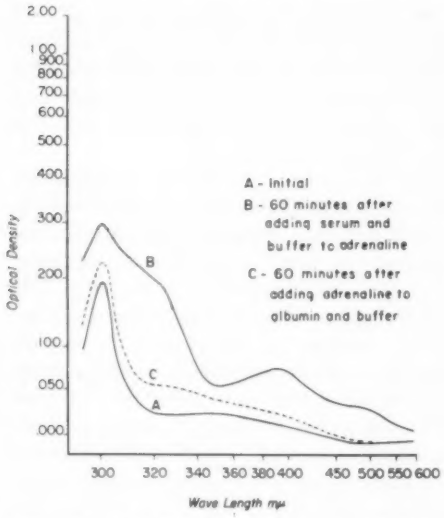
the routine oxidation test with whole serum. In Column 2 results are listed when serum is employed after ceruloplasmin is extracted. Results in Column 3 are those obtained when, as a substitute for 1.0 ml. of serum, the quantity of albumin contained in 1.0 ml. of serum is reconstituted with 1.0 ml. of isotonic saline. Column 4 lists the values obtained when the amount of ceruloplasmin from 1.0 ml. of serum is added to serum minus the ceruloplasmin q. s. to make 1.0 ml. The values obtained in the various procedures for individual subjects indicate that when ceruloplasmin is removed, the speed of oxidation is much decreased over the amount obtained by the routine procedure employing whole serum. When the albumin from 1.0 ml. of serum is employed, results are virtually the same as those obtained with serum minus ceruloplasmin. When ceruloplasmin is added to the serum from which it has been extracted, the speed of oxidation is virtually the same as that obtained with whole serum. In no instance was the variation more than 6%. These findings suggest that in the in vitro oxidation of adrenaline, ceruloplasmin is the important oxidizing substance and albumin is the important inhibitor in the reaction.

The data given in Table 2 show the results obtained using the above-described technique for a group of 12 hospitalized schizophrenic patients not receiving somatic or pharmacological treatment. The in vitro oxidation of adrenaline added to the serum averaged 0.184, a value which is significantly higher than that observed in the normal group, as given in Table 1. This finding

TABLE 2.—*In Vitro Oxidation of Adrenaline*: Schizophrenic Group*

Control No.	Optical-Density Differences Between the 60-Minute Curve and the Initial Curve				Amount of Cu in Ceruloplasmin Fraction, γ/100 Ml. Serum
	Using Whole Serum	Using Serum Minus Ceruloplasmin	Using Albumin Only	Using Ceruloplasmin plus Albumin and Globulin	
1	0.119	0.012	0.011	0.122	150
2	0.105	0.012	0.010	0.107	140
3	0.147	0.014	0.014	0.145	175
4	0.160	0.027	0.020	...	192
5	0.169	0.018	0.000	0.167	192
6	0.187	0.011	0.017	0.186	220
7	0.197	0.026	0.020	0.199	227
8	0.210	0.033	0.034	0.211	242
9	0.218	0.023	0.020	0.217	253
10	0.231	0.030	0.028	0.229	265
11	0.230	0.027	0.020	0.229	265
12	0.239	0.016	0.015	0.239	274
Averages:	0.184	0.021	0.017	0.180	216

* In each instance 1.0 ml. of solution is employed against 1.0 ml. of adrenaline (2 mg/ml.). For explanation of Table, see "Results."



Figs. 1 and 2.—Illustrative curves from Subject as obtained on Beckman DK spectrophotometer. On each Figure, Curve *A* is the spectrum obtained at one minute, after the addition of 1.0 ml. of adrenaline (2 mg.) to 1.0 ml. of serum and 1.0 ml. of buffer. Figure 1 (left): Curve *B* is the spectrum obtained with this solution after 60 minutes. Curve *C* is the spectrum obtained 60 minutes after the addition of 1.0 ml. of adrenaline (2 mg.) to 1.0 ml. of albumin and 1.0 ml. of buffer, showing inhibition of oxidation.

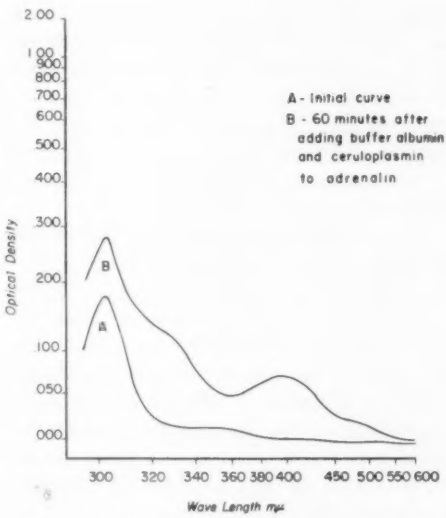


Figure 2 (right): Curve *B* is the spectrum obtained 60 minutes after the addition of 1.0 ml. of adrenaline (2 mg.) to 1.0 ml. of albumin, globulin, and ceruloplasmin (reconstituted serum) and 1.0 ml. of buffer. This curve compares closely with Curve *B* (Fig. 1), where whole serum was utilized.

also agrees with the results obtained previously from this laboratory.[5] It is interesting to note that the albumin fraction obtained from the schizophrenics is almost identical with that obtained from the normal group in its quality of inhibiting the oxidation of adrenaline in this test. The quantities of albumin in the sera from the normal and schizophrenic groups are virtually the same, each averaging approximately 5%. We found, in addition, that rather marked variations in the amount of albumin in the solution used did not significantly alter the curve obtained on the spectrophotometer. Even solutions containing as high as 20% albumin produced the same degree of inhibition as those containing only 5%. When the ceruloplasmin fraction was added to the serum minus ceruloplasmin, the original curve expressing speed of oxidation for each individual patient was virtually reproduced.

In the fifth, and last, column on each Table, the calculated value, in micrograms, of copper bound to ceruloplasmin for 100 ml. of serum is presented. For the control group, the average value is 122γ per 100 ml. of serum, which closely compares with the previously reported values of 110γ per 100 ml.[10] In the schizophrenic group, the average value is 216γ per 100 ml. of serum, or practically twice the average amount of copper found in the normal group. For comparing the figures presented for total copper with the optical-density figures indicating speed of oxidation, it will be noted that there is a close parallel between the two sets of values, those with lower amounts of copper presenting lower figures for oxidation and those with higher copper values showing increased speeds of oxidation.

Comment

Recently, considerable attention has been focused upon the role that altered adrenaline metabolism might play in schizophrenia.

Hoffer and associates || have suggested that the presence of adrenochrome, a known oxidation product of adrenaline, might be responsible for psychotic behavior. Rinkel and colleagues [12] speculate that adrenoxine, another oxidation product of adrenaline metabolism, may be implicated in psychotic behavior.

Various authors have reported differences between normals and schizophrenics in biochemical measurements. Altschule [13] and Ljungberg [14] studied glutathione levels in mental disease and noted some correlation between schizophrenic behavior and blood levels of glutathione. Altschule and associates ¶ have also described alterations in sugar metabolism. In separate publications we presented findings of altered glutathione levels in schizophrenic patients which were similar to those reported by the above authors and also presented data showing that frequently the speed of oxidation of adrenaline was greater in schizophrenic patients than in normals in the absence of other disease processes.# However, in both our studies we noted that similar changes in both these indicators were present also in the blood of patients with various chronic intercurrent disease processes, especially when serum globulins were elevated, and that these changes appeared, therefore, not to be specific for schizophrenia. Lahey and co-workers [7] reported increases in ceruloplasmin in association with a variety of disease processes, including leukemia, Hodgkin's disease, hemochromatosis, aplastic or primary refractory anemia, and hyperthyroidism and, to a less severe degree, in a variety of additional diseases. Cartwright and associates [8] also reported increases in ceruloplasmin in schizophrenia. Since ceruloplasmin, an oxidase containing copper and a globulin, was known to produce alterations in glucose metabolism and was known to oxidize glutathione, we were interested in determining whether it played a role in the oxidation of adrenaline. The date presented support this contention.

There are several studies concerning adrenaline oxidation reported in the literature. Schacter [17] has presented evidence for an oxidizer of catechol but specifically states that this did not oxidize epinephrine. He employed the Warburg apparatus for measuring oxidation. We elected to use the Beckman DK spectrophotometer because we felt it would be a more sensitive indicator. Schacter did not report the isolation of the responsible enzyme. He likewise presented evidence of the presence of an inhibitor of catechol oxidation. Our data suggest that the inhibitor of adrenaline oxidation is albumin.

Holmberg [18] states that the P-1 fraction of serum, identified as containing a copper globulin—the compound which was later named ceruloplasmin—did not oxidize adrenaline. At that time he employed the Warburg apparatus, which we believe is not sufficiently sensitive to detect the oxidation. In 1951 Holmberg and Laurell [19] stated that adrenaline was oxidized more rapidly by pregnancy serum than in the presence of serum from the umbilical cord. It is known that pregnancy serum contains much higher levels of ceruloplasmin than does the serum from the umbilical cord.[20] Holmberg and Laurell speculate, but do not present evidence, that the difference in speed of oxidation between the two sera is due to higher levels of ceruloplasmin in the pregnancy serum. Several authors * report increased levels of serum copper in schizophrenia. Since, with the exception of Wilson's disease, 96% of copper in serum is in ceruloplasmin, this indicates elevated ceruloplasmin levels.

Our data suggested to us that oxidizing enzymes may be of some importance in the understanding of a metabolic aberra-

|| Hoffer, A.: Adrenolutein as Psychomimetic Agent, paper delivered before a meeting of the American Physiological Society and the American Association for the Advancement of Science, Atlanta, Dec. 27-28, 1955.

Hoffer, Osmund, and Smythies.[11]

¶ References 15, 16.

References 5, 6.

* References 21, 22.

tion in the disease schizophrenia. The findings which relate the quantity of ceruloplasmin to the speed of oxidation, however, are not specifically related to schizophrenic behavior. They suggest the possibility that the oxidizing enzymes which are frequently, but not always (the principal exception being the chronic patients), quantitatively greater in schizophrenia may be qualitatively different in this disease process. This possibility has been explored, and a preliminary report has been made.[23] A more detailed report of this line of study is at present being prepared for publication.†

Summary

In this study we have attempted to isolate those substances which influence the speed of oxidation of adrenaline as determined in an in vitro test. Data presented indicate that ceruloplasmin, a copper globulin, is the important oxidizing substance and that albumin is an active inhibitor of this process.

†Leach, B. E.; Heath, R. G.; Cohen, M., and Martens, S.: Taraxein: Method of Extraction from Serum of Schizophrenic Patients and Identification Studies, in preparation.

REFERENCES

1. Heath, R. G., Editor: Studies in Schizophrenia, Cambridge, Mass., Harvard University Press, 1954.

2. Heath, R. G.: Correlations Between Levels of Psychological Awareness and Physiological Activity in the Central Nervous System, Psychosom. Med. 17:383, 195,.

3. Bellak, L.: Dementia Praecox, New York, Grune & Stratton, Inc., 1948, Chap. V.

4. Heath, R. G., and Leach, B. E.: Multidisciplinary Research in Psychiatry, in Changing Concepts of Psychoanalytic Medicine, edited by Sandor Rado and George E. Daniels, New York, Grune & Stratton, Inc., 1956.

5. Leach, B. E., and Heath, R. G.: The in Vitro Oxidation of Adrenaline in Plasma, A. M. A. Arch. Neurol. & Psychiat. 76:444, 1956.

6. Martens, S.; Leach, B. E.; Heath, R. G., and Cohen, M.: Glutathione Levels in Mental and Physical Illness, A. M. A. Arch. Neurol. & Psychiat., to be published.

7. Lahey, M. E.; Gubler, C. J.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Copper Metabolism: VII. Blood Copper in Pregnancy and Various Pathologic States, J. Clin. Invest. 32:329, 1953.

8. Cartwright, G. E.; Huguley, E. M.; Ashenbrucker, H.; Fay, J., and Wintrobe, M. M.: Studies on Free Erythrocyte Protoporphyrin, Plasma Iron and Plasma Copper in Normal and Anemic Subjects, Blood 3:501, 1948.

9. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1955, p. 1468.

10. Holmberg, C. G., and Laurell, C. B.: Investigations in Serum Copper: II. Isolation of the Copper Containing Protein, and a Description of Some of Its Properties, Acta chem. scandinav. 2:550, 1948.

11. Hoffer, A.; Osmond, H., and Smythies, J.: Schizophrenia: A New Approach, J. Ment. Sc. 100:29, 1954.

12. Rinkel, M.; Hyde, R. W.; Solomon, H. C., and Hoagland, H.: Experimental Psychiatry: II. Clinical and Physio-Chemical Observations in Experimental Psychosis, Am. J. Psychiat. 111:881, 1955.

13. Altschule, M. D.; Siegel, E. P., and Henneman, D. H.: Blood Glutathione Levels in Mental Diseases Before and After Treatment, A. M. A. Arch. Neurol. & Psychiat. 67:64, 1952.

14. Ljungberg, E.: Some Observations on Behavior of Blood Glutathione, Particularly During Insulin Shock Treatment, Acta psychiat. et neurol. scandinav. (Supp.) 47:182, 1947.

15. Altschule, M. D.; Henneman, D. G., and Goncz: Effect of Intravenous Administration of Glutathione in Man on Blood Glucose, Some Other Blood Carbohydrates and Serum Inorganic Phosphate, Metabolism 4:433, 1955.

16. Altschule, M. D.; Henneman, D. H., and Goncz: Carbohydrate Metabolism in Brain Disease, A. M. A. Arch. Int. Med. 95:594, 1955.

17. Schacter, B.: Serum Catecholase: Properties of the Enzyme and Nature of an Endogenous Inhibitor, J. Biol. Chem. 184:697, 1950.

18. Holmberg, C. G.: On the Presence of a Laccase-like Enzyme in Serum and Its Relation to the Copper in Serum, Acta physiol. scandinav. 8:227, 1944.

19. Holmberg, C. G., and Laurell, C. B.: Oxidase Reactions in Human Plasma Caused by Coeruloplasmin, Scandinav. J. Clin. & Lab. Invest. 3:103, 1951.

20. Fay, J.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Free Erythrocyte Protoporphyrin, Serum Iron, Serum Iron-Binding Capacity and Plasma Copper During Normal Pregnancy, J. Clin. Invest. 28:487, 1949.

21. Brenner, W., and Breier, E.: Zugleich ein Beitrag zur Kenntnis der kindlichen Schizophrenie, Ztschr. Kinderh. 66:620, 1949.

22. Heilmeyer, L.; Keiderling, W., and Stüwe, G.: Kupfer und Eisen als körpereigene Wirkstoffe, Jena, G. Fischer, 1941.

23. Heath, R. G.; Leach, B. E.; Martens, S., and Cohen, M.: Studies in Mind-Brain Relationships, Behavioral Changes with Administration of Taraxein, a Substance Extracted from Schizophrenic Serum, New York, Grune & Stratton, Inc., to be published.

Receptor Preferences in Schizophrenic Children

WILLIAM GOLDFARB, M.D., Ph.D., New York

The schizophrenic child characteristically presents a remarkable array of symptoms. Indeed, the breadth of symptomatology and the extreme degree of divergence from normality in virtually all regulative and coordinative activities are almost diagnostic signs in themselves. Widespread disturbances seemingly occur at all levels of integration and affect all psychic functions. A proper delineation of the disorder, therefore, will emerge eventually from investigation of all dimensions of behavior.

Receptor processes, however, are of special interest. Through these processes, the child attains an understanding of his internal and external worlds. They also form the foundation for responding to these worlds. For some time, it has appeared that one of the major trends contributing to the globally bizarre picture of the childhood schizophrenic is a deviant pattern of receptor activity. In the past two and one-half years at Ittleson Center, therefore, a systematic and focused clinical interest has been in the receptor behavior of early-school-age schizophrenic children. Direct observation has been made of a group of these children as they live in the Center and in the controlled confines of the medical clinic, treatment playrooms, and observation laboratory. In addition, counselor and parent reports of their observations of the children's daily responses have been recorded. Most detailed observations have been made of the children in residence, but we have also had opportunity to observe a larger body of children whose parents have applied for their admission. In intake processing, too, we have had the opportunity to read several hundred referral histories, with our special interest in receptor patterns in mind. These observations have served to buttress early impressions and to refine hypotheses leading to subsequent experimental study. For the present, this report is primarily a descriptive summary of observations with illustrative material.

Received for publication May 7, 1956.

Director, Henry Ittleson Center for Child Research.

This report represents Serial Publication No. 6 of the Childhood Schizophrenia Project of the Henry Ittelson Center for Child Research, under support by The Commonwealth Fund and the Ittelson Family Foundation.

The Central Hypothesis: Distance and Contact Receptor

In his classical work, "The Integrative Action of the Nervous System," Sherrington [11] provided a simple but brilliant model within which to order receptor experience. It will be recalled that he described the two varieties of distance and nondistance receptors. Distance receptors are receptors which react to objects at a distance. Nondistance receptors react to objects in close proximity or in contact with the organism. In this discussion the latter will be called the contact receptors.

The Distance Receptors: Vision, Hearing

On the basis of observations, it is proposed that in childhood schizophrenia there is an alteration in the usual hierarchy of receptor preferences and in the relationship of the various sensory modalities. The most important observation was the diminished use of the distance receptors, sight and hearing, by schizophrenic children. Ordinarily, there was no evidence of a significant defect in visual and auditory acuity or in visual or auditory thresholds. Rather, the behavior suggested visual and auditory

avoidance or inattention. Such inattention, in effect, caused the schizophrenic child psychologically to be a nonhearing, nonseeing child. Clinically, this was demonstrated in the glassy, nonseeing stare of these children. The observer found himself unable to achieve visual contact with them. The child seemed to look through anyone approaching frontally or to avoid direct visual contact entirely by averting gaze. An interesting sign was that of persistently dilated pupils when the child was faced close to. When approached frontally, the children were given to short glances and eye-roving rather than to regarding or "grasping" sustainedly with the eye, i. e., eye fixation and pursuit. The children had unusual difficulty in looking sustainedly through small apertures, as of telescopes or microscopes. The poorly sustained and brief visual glances, when they occurred, were often accompanied by tactile maneuvers, such as touching with the hands, or lips, or even tongue. At such time the visual glances appeared unfocused and less dominant than the touching.

Auditory inattention and avoidance were also readily observed. Some of the children did not react to auditory stimulation at all (Observation 1).

Observation 1.—James was typical of many autistic children. A sharp noise near his ears, for example, sharp hand clapping, produced only eye blinking. There was no other body or facial adjustment and no verbal indication that the sound was recognized. In one period of observation, the noises near his ears were repeated again and again for an hour without any overt adjustive response, such as avoidance by moving away, or verbal and vocal complaint and objection, or aggressive retaliation.

Some of the children could only be reached by very loud noises (Observation 2).

Observation 2.—While in a phase of acute catatonic withdrawal, Joyce stared but did not fixate. A hand passed in front of her eyes on a direct head-on approach produced no response of awareness. Her counselor complained, "I have to get on top of her and make a loud noise for her to show any kind of response." A loud voice facilitated contact with her and efforts at stabilization. At times she would scream without apparent cause. If the counselor yelled loudly, "What are you doing?" she would stop her screaming.

Counselors and teachers referred to possible deafness. Thus, in diagnosis, there was a frequent need to differentiate autism from deafness. Otological examination has become routine at the Center. The problem of diagnosis of auditory acuity among the schizophrenic children has been significant enough for us to explore special methods for evaluating auditory thresholds, such as the conditioning techniques utilized with infants.

Five out of 16 schizophrenic children under observation at times actively excluded sounds by covering their ears with their hands and fingers or by lifting their shoulders to their ears. These children were obviously hypersensitive to auditory stimulation (Observation 3). They were akin to the small group of children, described by Bergman and Escalona,[1] with unusual sensitivities in several, occasionally in all, sensory modalities.

Observation 3.—Ever since birth, Mary, age 9, has been unable to tolerate strong stimuli of any kind. Noises have continued to produce startle reactions up to the present. She frequently complains, "It's too noisy," and covers her ears in a panicky, disorganized fashion. At one point, she was noted to object to bright lights. Her mother states she has always been intolerant of cold or heat.

The Contact Receptors: Touch, Taste, Smell

In contrast to their diminished use of the distance receptors, the schizophrenic children were more inclined than normal children to explore the environment through their contact receptors. Exaggerated hand touching and manipulation were common. Many parents complained that the children could not keep their hands off their surroundings. Various parts of the hand were favored. Some used delicate finger touching. Others felt grossly or tapped with the whole palm or surface. One child tapped with the backs of his fingers. He was also inclined to pinch what came into his hands or would let objects slip gently through his fingers.

The hand was not the only part of the body used for touch. The cheeks, forehead, lips, tongue, and all of the inner surface of

the mouth were employed (Observation 4).

OBSERVATION 4.—Paul was a child who initially removed himself entirely from the group and would sit for long periods fingering a small object. A period of residential treatment produced a definite improvement in range of affectivity and social engagement. He became attached to several members of the staff. He would sit in their laps and pass his lips over their faces and exposed body parts. This act had none of the qualities of a kiss and seemed to combine pressing and touching.

Loose exploratory mouthing of everything that could be put into the mouth was noted in some of the children. Looseness in muscle tone of the lips and mouth structures has always been an impressive finding in our clinical observation of schizophrenic children. This manifests itself in exaggerated drooling and lalling speech. In exploratory mouthing, the objects may be permitted to fall out as passively as drooling saliva. It is of interest that the oral receptor preference is not accompanied by increase in muscular tone and executive or coordinative proficiency of the mouth structures. The limp, atonic mouth accompanies the general absence of body tone and coordination. However, it appears to be linked also with absence of assertive, organized, efficient mouth grasping, biting, chewing, and swallowing. Rather, it is more likely to be accompanied by a total attitude of passivity and inactivity (Observation 5).

OBSERVATION 5.—Joyce had stopped eating. She wanted only to lie in a fetal position with eyes covered. She would burst into uncontrollable screams and whimper, "I want my mommy." Her loss of interest in eating and drinking became a hazard as she reached a state of dehydration and malnutrition. She was then fed by her favorite counselor. However, she would not bite or chew. She could be given fluids. However, in drinking, too, there were very inadequate and slight movements of her lips, tongue, and pharyngeal structures, so that the fluid was literally poured down her throat. Much of it, of course, dribbled out of her mouth.

The use of the mouth as the essential vehicle for receptor activity was sometimes accompanied by exaggerated drive to oral ingestion and incorporation (Observation 6).

OBSERVATION 6.—Peter would eat enormous quantities of food without stopping unless limited by the counselor. He appeared never to reach or experience satiation. He would consume his own food and all within reach. The other children had to guard their food lest Peter eat it with such rapidity that he could barely be observed.

More frequently the drive was toward sucking (Observation 7).

OBSERVATION 7.—Jane astounded everyone by her exaggerated, never gratified sucking drive. She sucked her fingers, lollipops, clothes, and anything within reach.

At times, the incorporative trend was markedly evident in the way that the children structured their efforts at relationship (Observation 8).

OBSERVATION 8.—Tina sucked everything within reach. She also had an exaggerated wish for petting and body contact with her counselor. She would envelop the counselor physically in an octopus-like fashion by twisting her arms and legs about the counselor. Then she would suck the exposed arm or neck of the counselor. It was difficult to detach her from her counselor, whom she seemed to be using as a massive breast. As she improved clinically, she remained very possessive and jealous. She gave up the sucking relatedness and direct body seeking but would watch her counselor with fixed, intense gaze.

A very common mode of sensory activity was active smelling and sniffing. Though olfaction is a distance receptor in animals, the sniffling of the schizophrenic children was of an order of proximal or contact sensation. The object being explored was brought close to the nose, whether it was food, inedible object, own body parts, or body parts of others. It is possible, too, that the smelling was closely linked to tasting and was an aspect of the oral incorporative trend of the schizophrenic children.

The Relationship Between Distance and Contact Receptors

The global picture of childhood schizophrenia includes a constant and reciprocal relationship between the distance and the contact receptors. One may refer to a hierarchy of receptor or sensory preference. Distance receptors are avoided, and contact receptors are preferred. Following is a brief description in which the hierarchical ordering of sensory preference is demonstrated in the same child (Observation 9).

OBSERVATION 9.—Jane's counselors refer with exasperated amusement to the way she smells and mouths everything given to her. In one observation she was given a paper and pencil to draw a picture with. She smelled both objects. Then she scribbled on the paper without once looking at the paper and without once showing a fixed regard.

In our longitudinal studies of the children in treatment, we have been impressed by the fluidity of all their symptoms. So, too, the unique hierarchical ordering of sensory preference among the schizophrenic children was impressively flowing and frequently reversible. The dominance of the contact receptors was most evident among the schizophrenic children with the lowest level of ego organization, although residual elaborations of the touching and smelling could be found among the most highly integrated schizophrenic children. The conspicuous emergence of the schizophrenic pattern of sensory preference was seen in children as they moved into clinical states of acute panic, withdrawal, and regressive disorganization (Observation 10).

OBSERVATION 10.—Joyce was a completely isolated little girl. She would wander aimlessly or lie on her bed masturbating constantly, without any apparent awareness of her surroundings. Her counselor noted: "Joyce is always sucking on something. She will eat as much candy as I give her, sucking rather than chewing. She sucks on her clothes. At times, when I sit down to talk to her, she constantly has her hands on me, moving them over my hair, my neck, my breast, and my arms." Her avoidance of visual and auditory stimuli during a phase of acute catatonic withdrawal has been noted (Observation 2). During this episode, she would cover her eyes actively and would stand with her eyes shut, as though sleeping. She would go to bed right after supper, lie in a fetal position, and pull the blankets over her head. She took everything into her mouth without discrimination. She had an unseeing gaze (and yet did mold on body contact when enveloped). She was inclined also to lean against the wall, or to sink to the floor. She developed the mannerism of bending the upper half of her body at a 90-degree angle with the legs. This mannerism appeared to include the inclination to contact the floor with her body. In addition to her exaggerated mouthing, she was noted to smell the baseboards of the floor. Her total disturbance in integrating perceptions was reflected in an aberrant response to pain. She was found sitting without reaction on a hot radiator.*

On the other hand, as the schizophrenic child improves clinically, there is a reversal of the pathological perceptual pattern. The child begins to make more extensive use of the distance receptors and diminished use of his contact receptors. This was clearly shown in the following case of Keith, who showed very conspicuous improvement after about two and a half years of treatment (Observation 11).

OBSERVATION 11.—When Keith arrived at the Center, he avoided all direct visual engagement with anyone. He would look away if approached or bury his head to avoid looking. Similarly, he was unresponsive to auditory stimulation. He could not be reached by voice. He sniffed and smelled exaggeratedly so as to look very bizzare. He was given to compulsive and ritualistic patting of his body, clothes, belongings, and environment. He clung to walls and would select a bench on which he sat for hours and days unless forcibly moved. Similarly, he would straddle his counselor with his whole body at times, and would scream with rage at the counselor's efforts to disentangle him.

From birth, he was hypersensitive to sound and any change in the surrounding visual scene. He showed an unusually enduring startle reaction and until recently had jumped wildly at sudden, even if slight, noises. In infancy, removal to his crib away from loud noises and changing visual stimuli was the only effective device for quieting him during his prolonged periods of uncontrollable panic and screaming.

At 5 years of age, he was considered deaf by his counselor at a day camp. His auditory inattention at this time was so extreme that contact with him was made only by turning him around physically, facing him, holding him by the elbows, and talking loudly to him. Through this same period, however, he showed hypersensitivity to sound, with expression of startle and panic. In addition, he would at times cover his ears actively. His mother reported that he did not listen to what was said, and yet he would complain, "I don't understand what you're saying."

Until six months ago, Keith was a vigorous thumb sucker. His mother claims that friends commented at his desperate search for his thumb from the earliest weeks of life. He resisted forceful weaning at 15 months, and for many months drained his bottle in a frenzied fashion. Until re-

* The unusual deviation of pain adjustment among schizophrenic children will be reported elsewhere.

cently, when tense, he would push his tongue in and out repetitively.

Keith showed remarkable progress in treatment, and it was possible to send him back home. At this time he demonstrated less need for direct body contact. Sniffing and repetitive patting were rare, though they did recur somewhat during states of apprehension. He would look directly at one and would not shy from conversation. Verbal approaches were quickly accepted, and he could concentrate on visual stimuli. His educational achievement jumped conspicuously. On discharge, he was definitely a hearing-seeing child.

Analysis of Receptor Processes in a Schizophrenic Child

There is much to be gained from a detailed analysis of the receptor patterns of one child. John is an example of a profoundly regressed schizophrenic child. He is 8½ years old at the time of writing and has been in the residential treatment unit for two and one-half years. His behavior has been observed with unusual detail.

A brief extract from his psychiatrist's notes gives an accurate description of him: "John is an attractive little boy with curly hair. He gives an almost angelic, cherubic appearance. He is out of contact with the real world, and has almost no ability to make use of the elements of reality. He is totally bewildered, and wanders about in almost an aimless way, without any direction. He touches everything in a fleeting, furtive manner and has no ability to use objects in any meaningful way. He is plastic, clay-like, and can be led anywhere. When picked up, he puts his hand to his mouth, smiles, and melts into the examiner's arms like a nursing infant. In a typical few minutes in the playroom, John would wander about, touch things, put things to his mouth, touch things with the back of his hand, pick up a toy, finger it, blow on it, and blow on his hand, meanwhile stepping over toys and breaking them as though oblivious to everything. There is much random singing, and occasionally a few phrases can be made out."

John's disease began insidiously at birth. Born after a normal pregnancy, he was described by his mother as a helpless, apathetic baby, doubled up in fetal position with his eyes closed. He was restless and colicky, would accept only small feedings, and vomited a great deal for six months. During the period preceding the acute onset of his illness he was easily frightened and withdrew quickly from other people. Apart from this, development in intellect, language, and psychomotor functions was normal.

Acute Onset of the Disease: Sensory Changes

At 2½ years of age, in an atmosphere of marked tension between his mother and an interfering grandmother, John was abruptly and totally abandoned by his enraged mother. He suffered an acute and rapid dissolution of virtually all regulative and coordinative functions. He seemed not to hear. Yet an airplane noise made him agitated.

Observations

Observation 12 represents a five-minute sampling of his behavior in the observation room with his counselor.

OBSERVATION 12.—John's counselor is seated at a table in the center of the observation laboratory. The door opens, and John is seen at the entrance to the room. The counselor removes John's coat. He does not look at the counselor. He walks and runs around the four walls of the room, slapping the wall with his hand. As he runs his hand along the wall, he glances rovingly at the wall. He opens the door, and the counselor says, "Close it." She hands him a stuffed animal. He does not look at it but instead puts it into his mouth. He opens the door and closes it on sharp verbal command to do so. He walks back and forth along the wall, slapping it with his open palm. He chews on the doll's ear. He walks back and forth along the wall, slaps the wall, puts his hands on his crotch. He puts his hand on the door knob. He glances about. He slaps the wall. He drops the doll. He does not respond to a series of verbal commands to pick up the doll. The counselor walks to him, grabs his hand, and pulls him toward the doll on the floor. He grasps the doll, does not look at it, puts it in his mouth, glances at the floor, slaps the walls as he walks back and forth. He walks to the mirror, licks the glass.

During this brief sampling of his behavior, John demonstrates clearly his characteristic receptor tendencies. He does not fixate visually. When he glances at the nearby surfaces of the wall, the visual glance is accompanied by touch. Similarly, he shows little response to the voice but does respond to loud verbal prohibition. His essential technique for exploration is repetitive tapping with his hand. Linked to this, also, is his use of his lips and tongue to touch surfaces and objects. An object placed in his hand is not brought to view by his eyes but, rather, is placed in his mouth. Manual prehension serves the mouth and not the eyes. He is also drawn repetitively to the walls. He appears to have a stereotropic orientation

to surfaces of contact.† John also molds to the bodies of humans who hold him and whirls with marked pliability when his head is turned lightly. These responses seem linked to his attraction to solid surfaces of contact.‡

There have been many opportunities to observe his visual reactions. Characteristically, he has always shown a roving glance. He does not fixate (Observation 13).

Observation 13.—During one period of observation in the office with one observer, a tally was kept of visual regards that fixated more than five seconds. Not once did he fixate visually for five seconds or more. He seemed not to be looking at anything. He ran and walked rapidly about the room along the walls, which he tapped repetitively with the back of his fingers. He would move in circular fashion. Again and again he would run until he bumped into a telephone wire which blocked his path. He had no visual awareness of the wire and showed a tactual response when it blocked him.

Observation 14.—At rest time, the counselor hands John a book. He thumbs through it carelessly but does not look at the pictures.

An enforced visual stimulus does not lead to the normal adaptive response (Observation 15).

Observation 15.—A flashlight is held directly in front of him. When the light is turned on, John does not blink. In a second flashlight experiment six months later, John is led into a dark room. The flashlight is turned on and directed into his eyes. Initially he blinks; but as the flashlight is brought to ½ in. from his eyes, there is no reaction.

John's reaction is to press his lips into the glass shield.

The visual inattention applies to people, as well as nonhuman objects (Observation 16).

Observation 16.—John was observed with his mother for 15 minutes. In this period he glanced at her twice in spite of his mother's fixed gaze on him throughout.

† This wall seeking and attraction to tactile contact with solid surfaces is remarkably similar to the typical stereotropic orientation of young rats to lateral surfaces of contact.[3]

‡ Without underestimating differences between children and animals, this behavior reminds one of the stereotropic tendency of rats to make physical contact with each other.[6]

Of course, John did not use vision to differentiate one human from another. Even his mother seemed vaguely perceived (Observation 17).

Observation 17.—During this visit, John did not look at his mother at all. She followed him as he wandered aimlessly. In the lounge he sat on the laps of other women and did not seem to differentiate them from his mother.

Observation 17 is of significance, since it also demonstrates that the pleasure associated with a tactile form of exploration and gratification is to "part objects." John here seeks out the specific joy of warm body contact. However, the response to the total and specific image of a mothering person is absent.

John's not hearing takes two forms, that is, active blocking of his ears or passive not-listening (pseudodeafness). Observation 18 was recorded by his counselor.

Observation 18.—Frequently, John plugs his ears with his forefingers. There are days when the slightest sound seems to annoy him—for example, a barely audible airplane or children talking. At other times he seems not to hear and he can tolerate a considerable amount of screaming and noise.

Both from his history and from our own longitudinal observation, it seems clear that initially there was hypersensitivity to sound. His eventual adaptation was a defensive exclusion of sounds by not listening.

Observation 19.—In listening to the radio, he is particularly apt to put his fingers to his ears when he hears human voices. Music does not have the same effect.

Observation 19 emphasizes an element of auditory selection and confirms the link between his auditory avoidance and the defect in his relationship to humans. One may presume that the danger, if such may be inferred, is channeled through the voice (Observation 20).

Observation 20.—Today John was sensitive to direct visual approaches. As one approached him, he covered his ears. This was repeated throughout the day.

As with so many autistic children, there is an apparent paradox between his avoidance of visual and auditory interaction and his quick acceptance of physical envelopment (Observation 21).

OBSERVATION 21.—John did not look at me or respond to my voice. However, I took him into my arms, and he fitted snugly against me. Then he sat in my lap and fingered my lapel. His body felt limp against me.

One may interpret, perhaps, a level of hedonic response restricted to the immediacy of body contact. However, there is a very low level of striving and environmental manipulation to secure pleasure (Observation 22).

OBSERVATION 22.—John seems to love to sit in a full bath, to be washed and dried. However, he is aimless in the preparations. He makes no attempt to participate in the washing. He touches towels and soap in a limp, hit-or-miss fashion, or he fingers the wash basin fleetingly, as he does many objects he passes in his wanderings.

Similarly, John is capable of ingesting huge quantities of food. However, he makes no active effort to secure the food, such as one ordinarily sees in states of acute appetite (Observation 23).

OBSERVATION 23.—Today ice cream was bought for the children. The counselor offers John the ice cream, with no apparent response. However, ice cream placed in John's mouth is immediately swallowed. John wanders about but continues to swallow all the ice cream put in his mouth by the counselor, who follows him.

The same absence of awareness of pleasure potential in his surroundings is shown in his reaction to toys or books (Observation 24).

OBSERVATION 24.—A book is put in John's hand. It falls loosely out of his hand. A ball placed in his hand fares similarly. A plastic doll is put in his hands. He brings it to his mouth and drops it without looking.

John's receptor preferences are linked to the problem one has in communicating with him. He responds chiefly to tactile engagement (Observation 25).

OBSERVATION 25.—John is in a room with his counselor. I open the door. The counselor is busy cutting and sewing. John is running back and forth along the walls. Though turned in my direction from time to time, he does not look at me. I cross the room and approach him closely, but he does not fixate on me. His eyes rove. I return to the other side of the room. I call him, using an ordinary speaking voice. There is no answer. I call his name loudly, and there is no response. When he opens the door of the room, however, I say sharply and loudly, "Close it," and he closes the door. He passes me and, in passing, taps me, with no change in expression. I reach out, hold him, and fondle him. At this point John smiles very definitely and pinches my hand. I playfully lift him up, and he reaches for my mouth and eyes.

It is clear that in order to contact him he must be physically engaged. When he is thus engaged, he explores by touching. In his touch, he investigates only parts of the human who had reached him.

Finally, it is a striking fact that John's sensory pattern is adequate to keep him from being hurt. He has never incurred serious injury, though the staff has at times held its breath (Observation 26).

OBSERVATION 26.—John was found wandering back and forth on a high ledge with a drop of about 6 ft. below him. He wandered back and forth on the thin ledge, using his hands and feet in a graceful, light fashion.

Comment

The expression receptor preferences is used as a term to describe a behavioral pattern rather than primary neurophysiological processes. Our methods are geared to observation of complex behavior. It is, of course, possible that among some schizophrenic children the unusual receptor pattern is a direct expression of altered neurophysiological processes.§

§ For example, one might speak of an upward shift in thresholds in the activating systems which parallel sensory processes (Magoun[6]; Heath[18]); or, again, one could interpret a rhinencephalic dominance.[9] One might, perhaps, refer to a recurrence of the archaic receptor processes linked to rhinencephalic activity, such as smell, touch, taste. A hypothetical relationship between the Klüver-Bucy monkeys[7] and schizophrenic children is attractive. In Klüver and Bucy's classical experiment, ablation of the hippocampus, uncus, and amygdala, as well as a major part of the temporal neocortex, produced dramatic behavioral changes in monkeys. Among these changes were sensory alterations that remind one of the schizophrenic children. The monkeys, for example, licked, chewed, and nuzzled all objects repetitively. These oral tendencies were combined with diminished ability to recognize the meaning of objects on the basis of visual cues, a strong tendency to react to every visual stimulus in the environment, remarkable changes in emotional behavior, and increased sexual activity.

However, our observations have more immediate bearing on the interactive and communicative relationship between the child and his world.

Our observations confirm the generalization that the childhood schizophrenic seems to lack interest in the outer world. He resists social engagement. He accomplishes this by cutting off the major perceptual channels used in normal social intercommunication, i. e., vision and audition, despite the fact that there is no detectable defect in the sensory apparatus and neuroanatomic substrate for hearing and seeing. Indeed, there is good evidence that the schizophrenic child can hear and see, but he does not look or listen. He does not use visual and auditory experiences, so that, in effect, he behaves as a nonhearing, nonseeing child.‖

Further confirmatory evidence of an experimental nature is again an incidental by-product of another study (Pollack, M., and Goldfarb, W.: Perception of Double Simultaneous Tactile Stimuli in Institutionalized Schizophrenic Children, paper read before the Eastern Psychological Association, March 23, 1956). A comparison was made of the reactions of schizophrenic and normal children between 7 and 9 years of age to M. Bender's neurological test of Double Simultaneous Stimulation (DSS). In one part of this test, the examiner simultaneously touches the face and the contralateral hand of the child, whose eyes are closed. Schizophrenic children make more errors in localizing the two touches than normals. Of special interest for the present discussion, however, was the following: With eyes open, no normal child made an error. However, 13 of 15 schizophrenic children continued to make errors even with eyes open. In the case of some of the children, there was apparent nonawareness of the hand stimulus even when the hand was touched while it was held up directly in front of the eyes.

To a varying degree, the neither looking nor listening is characteristic of all schizophrenic children, regardless of integrative and organizational level. On the other hand, the behavior is not rigid. The fluidity, even reversibility, of the pattern in individuals has been illustrated. There is considerable variation in the behavior of individual children, and the individual variation is distinctly influenced by the social setting. Thus the schizophrenic child can be seen to avoid looking and listening with some people but not with others.

Similarly, there is a great deal of individual variation in the use of the contact receptors. The most bizarre and exaggerated behavior of touching, mouthing, and smelling occurred among the least organized and most regressed children. Yet tapping did occur among some of the more organized schizophrenic children, although for them mostly in relation to magic rituals. Similarly, exaggerated sucking and overeating occurred independent of level of organization. Smelling and sniffing, too, were noted commonly among the schizophrenic children at all levels of ego organization.

Over-all, the schizophrenic child may be said to exclude perceptual experience in part or in totality. In such circumstances, the child fragments his perceptual world by selectively experiencing one part of the world rather than another. Thus, there may be a total exclusion of outer experience and preoccupation solely with the self; or there may be marked interest in nonhuman objects and total exclusion of humans from perception. The child might also narrow his sights to include his mother only, with a refusal to fixate on others. Again, there might be total avoidance of any human face as a source of visual and auditory stimulation. Undifferentiated experience with part characteristics of humans, such as, for example, body warmth and closeness, may be acceptable at the same time that visual and auditory stimuli are avoided.

The distance senses are inseparable from the functions of volition and attention. The normal child does more than merely see and hear. He looks and listens. By the fourth month of life the normal infant has an active visual organization,[4] an organiza-

‖ Dramatic confirmation of the basic hypotheses has recently been presented as an incidental by-product in a study of suspected deafness in children.[6] In this investigation, 50 preschool children referred to a hospital otolaryngological clinic for suspected deafness were studied psychiatrically. Fifteen of these children were shown to have no hearing loss. Seven of these fifteen pseudodeaf children were diagnosed as autistic.

tion that is absent among unstructured schizophrenic children of 7-9 years of age. The schizophrenic child's non-use of distance receptors, therefore, is a disorganization of human function, and not a mere regression to infantile levels of receptor activity.

The significance of the distance receptors in phylogenetic development has been emphasized.[10] Seeing and hearing are essential preconditions for anticipatory behavior. They accompanied the appearance of fear and rage in the evolutionary scale. In ontogenetic development, as well, an efficiently functioning pattern of attending to, and assimilating, visual and auditory stimuli is essential for the total coordinative and regulative effectiveness of the ego. The human being receives his most comprehensive information regarding his surroundings through his distance senses, but chiefly through vision. Vision records form, color, size, position, and distance all at once. In the absence of sight, perception through the other modalities is adversely affected. Thus, the touch perceptions of a blind child, of necessity, are limited in detail and restricted to the space within reach of his body.[3] Notions of space are attained through an interweaving of visual, tactile, auditory, vestibular, and kinesthetic reactions.[12] The integration of a body image in which the limbs are coordinated parts of the child's body is achieved largely through vision. Ideas of near and far are the consequence of coordinated impressions via manual touch and vision. One aspect of distance perceptors is their link to conative feeling, i. e., to striving and volition.[11] As such, the distance receptors help in integrating and in facilitating the purposive, planful adjustments of the whole person. They not only augment the range of perception but also permit quick perception of the whole situation. They are, therefore, prerequisite to giving the person a sense of continuity in the outer world. Obviously, external continuity is essential for the subjective experiencing of a stable, cohesive world. Further, experiencing a stable, continuing outer world is indispensable for the achieving of a definite personal identity, i. e., awareness of one's self as distinguishable from the outer world.

Schizophrenic children demonstrate the disabling consequences of defective use of, or even the disuse of, the distance senses. These children have difficulty in waiting, anticipating, planning, delaying gratification. They behave as if overcome by confusion and disorientation. Their focus is on themselves, so that they compulsively explore their own bodies without consciousness of social impact or reaction. In their human interactions, they often are limited to transactions with part objects, e. g., the breast, skin, body warmth, which offer immediate comfort through the tactile senses, and particularly to those experiences linked to oral incorporative exploration and tension release. They investigate restlessly and persistently, in the absence of continuity of the world and the self. They are often overcome by panic and agitation when small shifts in the situation are encountered. Their atypical sensory preferences interfere with their development of empathic responses to and with normals. Of course, their defective use of distance receptors blocks normal communication.

Though the observations which are the basis for this report suggest causation, they are insufficient to answer the question of how the deviant receptor pattern of the schizophrenic children developed. The receptor pattern may reflect a constitutional deficiency, or may indicate withdrawal from visuoauditory dangers. Some schizophrenic children give evidence of marked congenital sensory hyperreactivity, which may suggest a thin protective barrier against stimulation.[1] It seems more reasonable to postulate a nearly universal pattern of persistent persecutory reaction in which the schizophrenic child seems to demonstrate elementary and primordial feelings of omnipotence which were never resolved in the course of his relation to his mother and family. Perhaps, overcome by his frustrated rage, he is frightened by projected fear of as-

sault. In this type of child, danger is in the voice and in the visual glance, which, for him, can destroy and damage. Hence, to avoid such annihilation, he avoids or denies these stimuli.

Any child attends actively mostly to the pleasurable. The failure of the child to attend to specific receptor information may represent the absence of the facilitating action of pleasure in that receptor activity. A reasonable generalization, then, is that the absence of loved objects capable of offering pleasure produces emotional pessimism and diminished interest in the outer world, or, in reverse, an excessive preoccupation with self. The seemingly paradoxical acceptance of gratification by contact between the child's body and part objects and the avoidance of the look or sound suggest how the global mother is denied but her lap, or any lap, is accepted passively.

5050 Iselin Ave., Riverdale Sta. (17).

REFERENCES

1. Bergman, P., and Escalona, S.: Unusual Sensitivities in Very Young Children, Psychoanalyt. Study Child 3-4:333-352, 1949.

2. Crozier, W. J., and Pincus, G.: Stereotropism in Rats and Mice, J. Gen. Physiol. 10:195-203, 1926.

3. Cutsforth, T. D.: The Blind in School and Society, New York, American Foundation for the Blind, 1951.

4. Gesell, A. L.: Infant Development: The Embryology of Early Human Behavior, New York, Harper & Brothers, 1952.

5. Hamilton, H. C., and Matlack, H. H.: A Method of Studying the Modifiability of the Stereotropism in the Albino Rat, Psychol. Bull. 32:551-552, 1935.

6. Hefferman, A.: A Psychiatric Study of 50 Preschool Children Referred to Hospital for Suspected Deafness, in Emotional Problems of Early Childhood, Gerald Caplan, Editor, New York, Basic Books, Inc., 1955.

7. Klüver, H., and Bucy, P. C.: Preliminary Analysis of Functions of the Temporal Lobes in Monkeys, Arch. Neurol. & Psychiat. 42:979-1000, 1939.

8. Magoun, H. W.: An Ascending Reticular Activating System in the Brain Stem, A. M. A. Arch. Neurol. & Psychiat. 67:145-154, 1952.

9. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. 38:725-743, 1937.

10. Rado, S.: Hedonic Control, Action-Self and the Depressive Spell, in Depression, Paul Hoch and Joseph Zubin, Editors, New York, Grune & Stratton, Inc., 1954.

11. Sherrington, C. S.: The Integrative Action of the Nervous System, New Haven, Yale University Press, 1906.

12. Stern, L. O.: Psychology of Early Childhood up to the Sixth Year of Age, translated from the 3d Edition, revised by Anna Barwell, New York, Henry Holt & Company, 1924.

13. Tulane University, School of Medicine, Department of Psychiatry, and Neurology: Studies in Schizophrenia, R. G. Heath (Chairman) and others, Cambridge, Mass., Harvard University Press, 1954.

EEG During Electroconvulsive Therapy with Succinylcholine

THOMAS C. PIEKENBROCK, M.D.
ROBERT C. TAYLOR
and
DOROTHY R. BECKA, Hines, Ill.

Many electroencephalographic recordings on patients with epilepsy have been published and various types of seizure discharges have been identified; however, the type of discharge that occurs in man during a full-blown grand mal generalized tonic-clonic convulsion has not (insofar as we have been able to ascertain) been illustrated in any previous publication. The reason is not far to seek.

The "Atlas of Electroencephalography" (Gibbs and Gibbs[1]) contains many examples of seizure discharges of the "grand mal type," but these are all subclinical discharges. When convulsive movements occur, the electroencephalogram either is obliterated by artifacts arising from the mechanical movement or is so mixed with these disturbances that it cannot be reliably interpreted (Fig. 1). Sufficient amounts of curare or curare-like drugs which eliminate muscle and movement artifacts are commonly employed in animal experimentation, but they are not ordinarily justified in clinical experimentation.

However, if a drug were employed which had the curare effect but an effect of such a short duration that an electrically induced stimulation could be given during the period of relaxation without injury or risk to the patient, the seizure pattern in man could be further evaluated and studied in detail through all its phases. Such a drug, succinylcholine (Anectine), is now commercially available.

For the past two years electroconvulsive therapy at this hospital generally has been given in conjunction with premedication consisting of thiopental (Pentothal) sodium, atropine, and succinylcholine intravenously, and this is recognized as a standard procedure in many other hospitals. It was conjectured that the electroencephalographic seizure pattern may be more absolutely defined if tracings were made during electroconvulsive therapy in conjunction with this method.

Procedure

Fifteen patients were selected at random for this study. The only criterion used was that they were receiving electroconvulsive therapy as an indicated treatment for their psychiatric illness. The psychiatric diagnosis, number of previous treatments, age (24 to 40 years), duration of illness, etc., included quite a range of differences, but the electroencephalographic findings were uniform, and are, therefore, not dependent on patient selection.

Each patient was brought to the electroencephalographic laboratory in a fasting state. The patient was placed in a supine position, and electrodes were applied bilaterally to the frontal, temporal, parietal, and occipital areas. The ear lobes were used as a reference. A Grass Model 111-D eight-channel electroencephalograph was employed. Following this, a standard ECT rubber headband was applied with bitemporal ECT electrodes. A control tracing was made. The patient was then given a mixture containing 200 mg. of thiopental sodium and 0.02 mg. of atropine by rapid intravenous injection through a 20-gauge needle. With the needle still in place, syringes were changed, and 30 mg. of succinylcholine chloride was injected rapidly. Forty-five seconds after this injection was completed,

Received for publication July 25, 1956.

From Veterans Administration Hospital, Hines, Ill.

Present address (Dr. Piekenbrock): Medical Associates, 1200 Main St., Dubuque, Iowa.

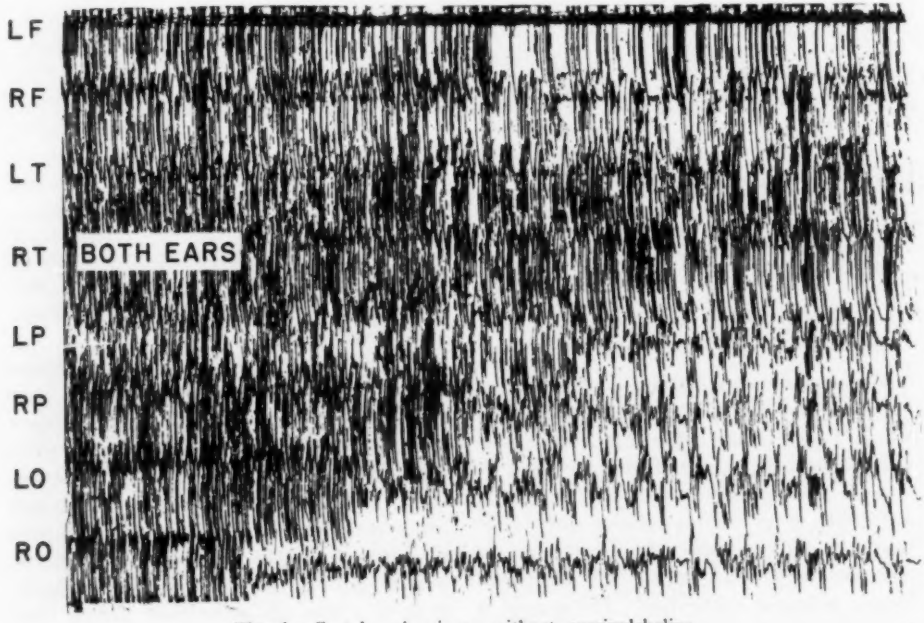


Fig. 1.—Grand mal seizure without succinylcholine.

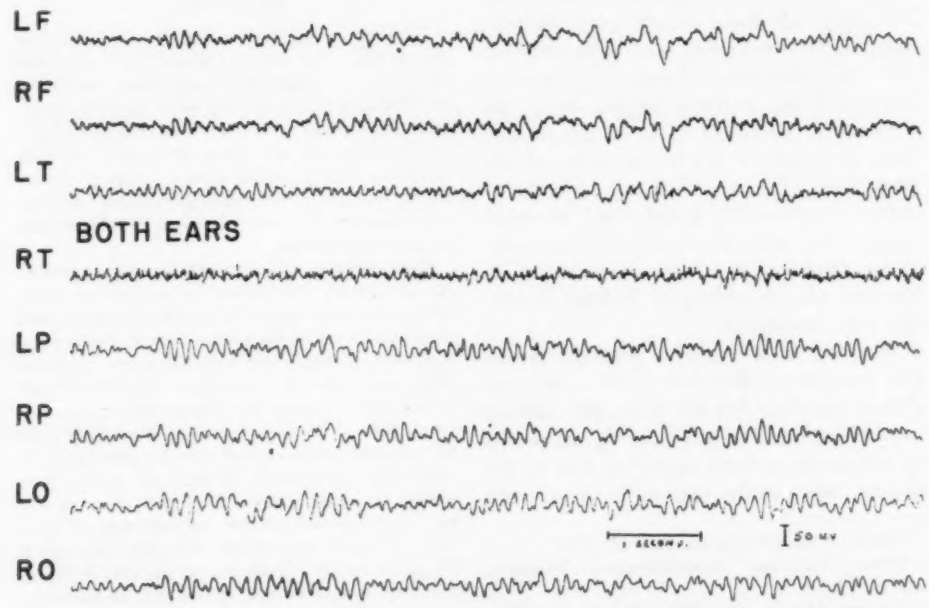


Fig. 2.—Control tracing before electroconvulsive treatment. Basic 9-per second activity; some bifrontal artifact and right temporal muscle.

the patient was given an electroconvulsive treatment, using the Medcraft Model B-24 electroconvulsive instrument preset at 110 volts, 1.0 second, with glissando. Electroencephalographic tracings were continuous during the whole procedure except that the writing pens were turned off for approximately two seconds during electrical stimulation because of 60-cycle interference. After treatment the patient was given 100% oxygen, using a mask with bag breathing. As soon as respiration became spontaneous, oxygen was discontinued and the electroencephalographic tracing was continued until the patient came out of the postseizure stupor.

ties were noted in the control period (Fig. 2).

After administration of thiopental sodium and atropine the record showed a generalized slow activity, which was irregular and of high voltage. This was mixed with lower-voltage fast activity (Fig. 3). This pattern continued until approximately 20 seconds after the succinylcholine was given, at which time muscle potentials were recorded in association with the generalized

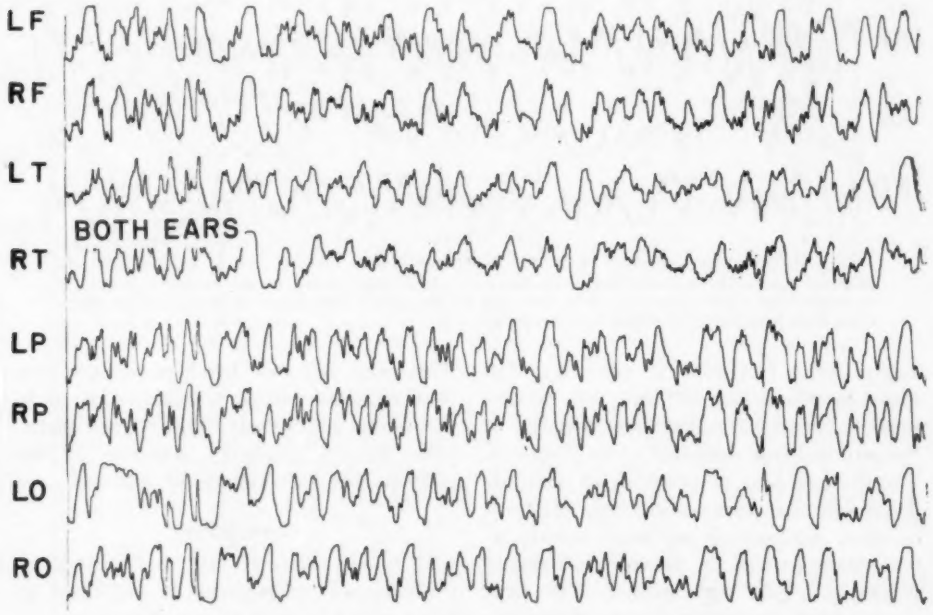


Fig. 3.—Generalized irregular, slow, 3-per-second activity occurring 15 seconds after rapid injection of 200 mg. of thiopental sodium to which is added 0.02 mg. of atropine.

Results

We did not extend this series beyond 15 patients because the results were consistent in all cases and it was felt that a larger group was not needed to substantiate the findings.

A control tracing of 5 to 10 minutes showed normal 9- to 10-per second activity in most cases, but in some patients who had previous electroconvulsive treatments the dominant frequency was 5 to 7 per second. Other than this slow activity, no abnormalimuscular twitchings (Fig. 4). This muscular activity was variable in duration but always appeared briefly and then disappeared. Muscle activity was entirely absent, and the patient was completely immobilized when the electroconvulsive stimulation was administered.

After 45 seconds, which has been recommended as the mean average for maximum muscle paralysis, the electroconvulsive treatment was given. Immediately after stimulation the electroencephalogram showed

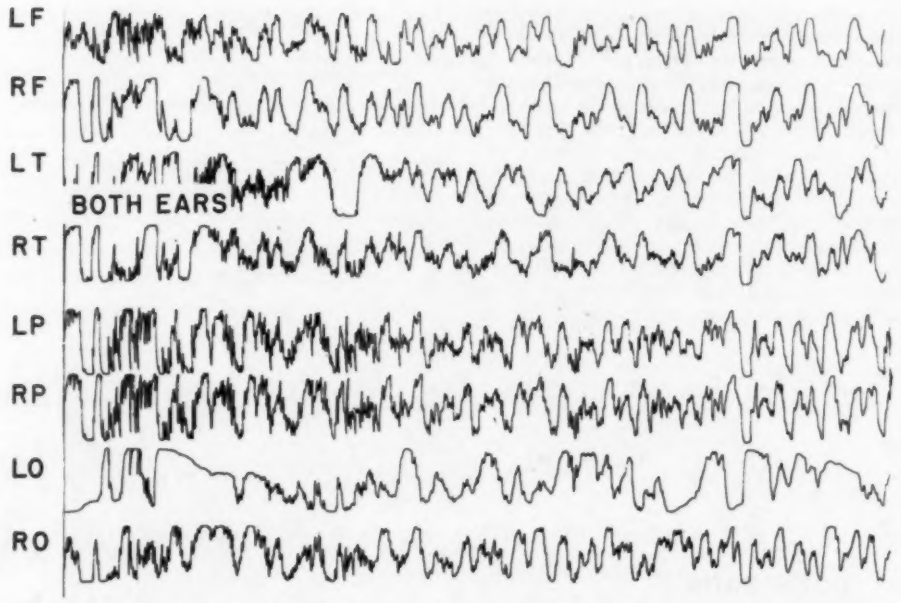


Fig. 4.—Following injection of 30 mg. of succinylcholine chloride muscle activity is superimposed upon the generalized slow activity. This was noted in all patients about 20 seconds after rapid injection. The last two seconds show cessation of generalized twitchings and beginning of muscular flaccidity.

fairly steady fast activity, which was followed by mixed fast and slow activity with many 3-per-second spike-dome patterns of the petit mal type discharge (Fig. 5, upper). This pattern was observed in all patients. There was no evidence at any time of a tonic or clonic movement or any motor manifestation on the part of the patient which would suggest a grand mal seizure. The pens writing from the temporal areas showed an electrical block of one to two seconds' duration immediately following treatment.

The 3-per-second spike-dome pattern continued for approximately 15 seconds, followed by an irregular spike and wave of a much slower frequency (Fig. 5, lower).

In this series oxygen was administered to most patients 30 seconds after electrical stimulation, and the high-voltage slow activity rapidly flattened; however, a few patients were not given oxygen, and this same flattening occurred approximately 30 seconds later, suggesting a refractory period following the convulsive seizure (Fig. 6). This was followed by high-voltage very slow irregular (stupor) waves of 1- to 3- per second in all leads (Fig. 7), and thereafter activity gradually returned to the previous preelectroconvulsive patterns.

Conclusions

It is our opinion that the method of studying seizure patterns as described in this paper has made it possible for us to see more clearly the actual cortical activity of the brain during electrically induced grand mal seizures. On the basis of this limited series we do not feel it is justifiable to draw any conclusions as to the significance of the electrical activity observed, which was of the petit mal type. We hope these observations will stimulate further research.

Summary

Electroencephalographic tracings were made on 15 psychiatric patients during electroconvulsive therapy premedicated with

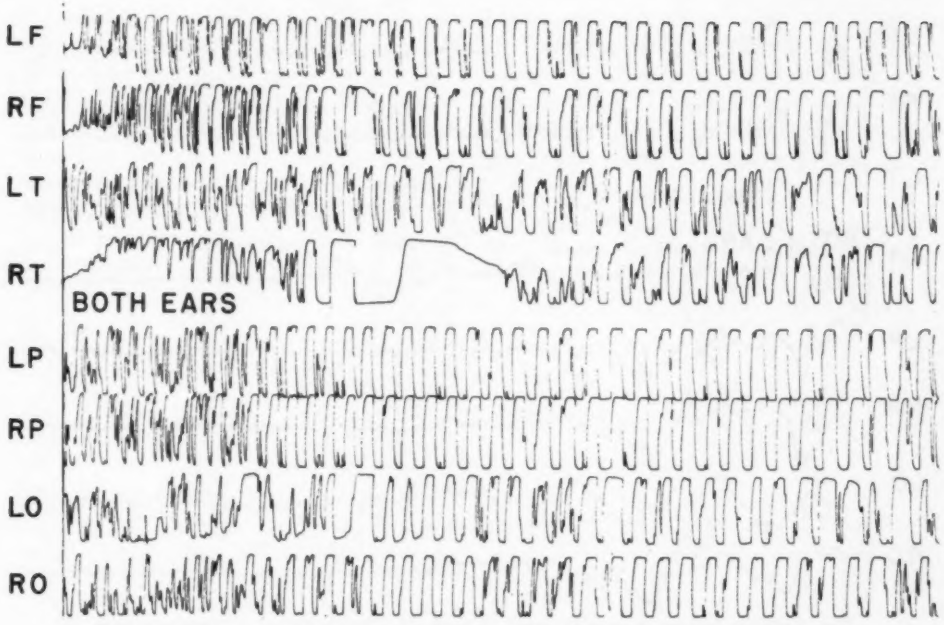
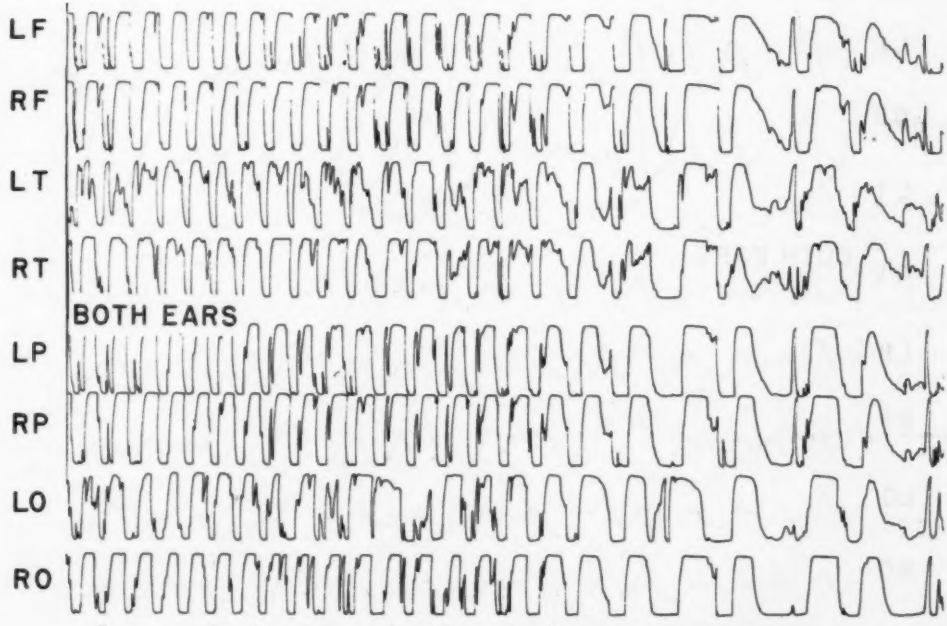


Fig. 5.—Upper, immediately after electroconvulsive stimulation, steady fast activity followed by mixed fast and slow and many spike and slow-wave patterns, often suggesting 3-per-second spike-dome activity of the petit mal type. During the seizure discharge there was no muscle movement, and the EEG shows no muscle activity.



Lower, continuation of the tracings above, showing patterns becoming slower.

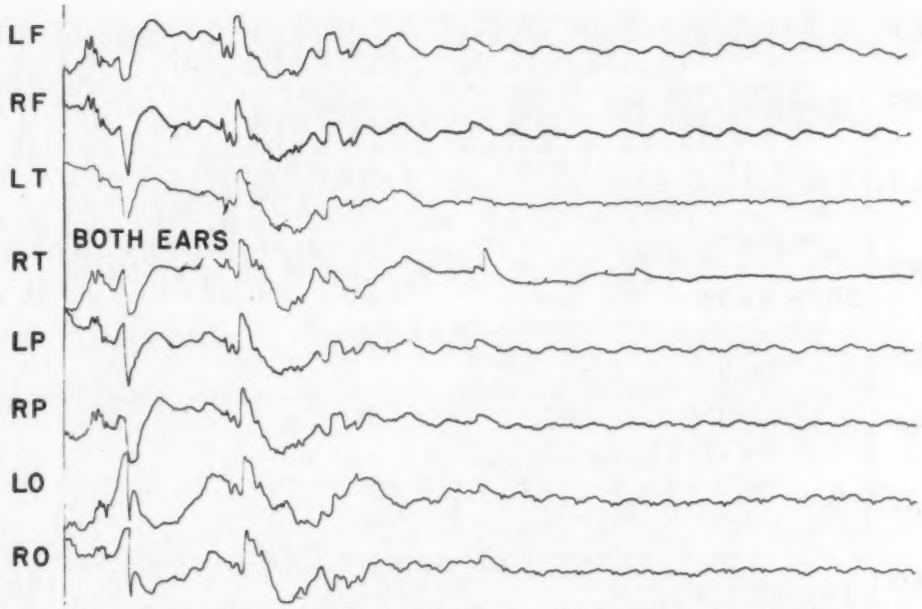


Fig. 6.—Flat pattern appearing with or without administration of oxygen about 30 seconds after the electrically induced convulsion, suggesting a refractory period.

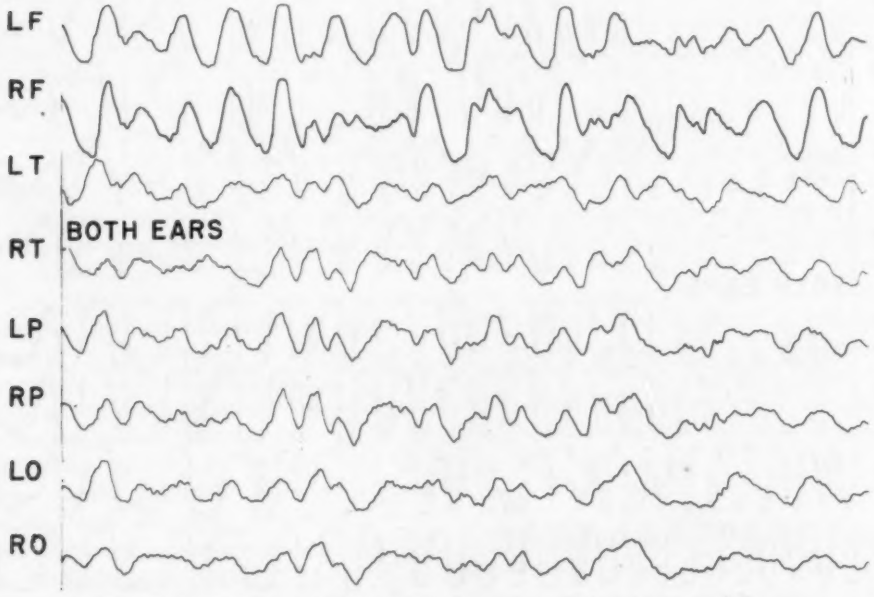


Fig. 7.—High-voltage 1- to 3-per-second slow waves during stupor period.

thiopental sodium and atropine and immobilized with succinylcholine.

The electroencephalographic changes consisted in the appearance of (*a*) high-voltage slow waves mixed with fast activity after thiopental sodium and atropine; (*b*) a transitory burst of muscle after succinylcholine, followed by disappearance of all muscle activity; (*c*) fast activity, followed by spike and wave patterns with a strong 3-per-second spike-dome component following electroconvulsive treatment; (*d*) a flattening of all activity with or without administration of oxygen 30 seconds after stimulation, and (*e*) irregular high-voltage slow waves during the stupor period.

REFERENCES

1. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Addison-Wesley Press, Inc., 1952.

Discharge and Readmission Among Mental Hospital Patients

A Cohort Analysis

J. M. WANKLIN, B.A.
D. F. FLEMING, M.A.
CAROL BUCK, M.D., Ph.D., D.P.H.
and
G. E. HOBBS, M.D., M.P.H., London, Ont., Canada

Purpose and Method

The strain currently being placed upon mental hospital facilities by ever-increasing numbers of first admissions[1] accentuates the need for a full understanding of the conditions most conducive to the early and permanent discharge of these patients. In the present study one approach to the fulfilment of that need was explored.

To assess the influence of certain variables upon probabilities of discharge and readmission, a cohort of mental hospital patients was followed in retrospect for 10 years after first admission.

The cohort was a stratified random sample of 240 patients, drawn from 831 patients first admitted to the Ontario Hospital, London, during the years 1940 to 1942.

The sample was stratified by four variables—age (ages 15-44, 45-64, 65+), sex (male, female), marital status (married, not married), and environment (rural, urban). Ten patients, randomly selected from those of the 831 who were applicable, comprised each of 24 strata, or subsamples, which together represented all combinations of the bracketed categories. By the numerical balance thus achieved, the four variables were automatically cross standardized.

A detailed description of the statistical method used to calculate probabilities of discharge and readmission can be found in an appendix. Briefly, a modification of the life-table technique was employed. Based only on the population still at risk, rates were calculated both of discharge at successive time intervals during the 10 years following admission and of readmission during the 9 years following discharge. The rates were then applied to a hypothetical cohort in order to derive probabilities cumulative to successive points in time.

Cumulative probabilities calculated in this way expressed the chance of discharge or readmission occurring if exposure to the risk of their occurrence was maintained during the period of time to which the probabilities applied.

The variables assessed were limited to those regularly reported in hospital case histories—the only accessible source of data. They were of two general kinds: those concerning socioeconomic status on first admission, and those concerning the course of events in hospital.

Results

A. Discharge and Readmission Probabilities—Their Relation to Time

1. *Total Sample* (Table 1).—(*a*) Discharge: Because discharge was customarily preceded by a six-month probation period, the discharge probability six months after admission (0.093) was necessarily slight. By the end of the first year, however, the probability had reached 0.437, the result of an intervening rate of discharge which was higher than at any other time.

The rate dropped notably after the first year and precipitously after the second. Consequently, the probability of discharge did not increase appreciably between the 2d year (0.605) and the 10th year (0.724).

(*b*) Readmission: Readmission occurred not at all during the first two months after discharge but reached its greatest rate during the next four months, resulting in a

Received for publication June 30, 1956.

From the University of Western Ontario Faculty of Medicine.

Mrs. P. Filer and Mrs. E. Reidy assisted in the preparation and analysis of the data.

This study was supported by a National Health Grant to the Mental Health Division, Department of Health and Welfare, and made possible by the Ontario Department of Health.

TABLE 1.—*Discharge and Readmission, Total Sample*

Discharge			Readmission		
Period After Admission	Rate per 100	Cumulative Proportion (Probability)	Period After Discharge	Rate per 100	Cumulative Proportion (Probability)
0 mo.	3.92	0.039	0 mo.	0.00	0.000
1 mo.	1.94	0.058	1 mo.	0.00	0.000
2 mo.	0.00	0.058	2 mo.	2.31	0.023
3 mo.	0.00	0.058	3 mo.	2.36	0.046
4 mo.	1.57	0.073	4 mo.	1.61	0.062
5 mo.	2.15	0.093	5 mo.	1.64	0.077
6 mo.	3.89	0.128	6 mo.	0.00	0.077
7 mo.	8.26	0.200	7 mo.	0.83	0.085
8 mo.	6.49	0.252	8 mo.	0.84	0.092
9 mo.	13.99	0.356	9 mo.	1.69	0.108
10 mo.	6.61	0.399	10 mo.	0.00	0.108
11 mo.	6.28	0.437	11 mo.	0.00	0.108
1 yr. 0 mo.	20.10	0.550	1 yr. 0 mo.	0.86	0.115
1 yr. 6 mo.	12.33	0.605	1 yr. 6 mo.	5.22	0.162
2 yr. 0 mo.	5.08	0.625	2 yr. 0 mo.	2.76	0.185
2 yr. 6 mo.	5.71	0.647	2 yr. 6 mo.	1.91	0.200
3 yr.	8.70	0.678	3 yr.	7.88	0.263
4 yr.	2.63	0.686	4 yr.	3.24	0.287
5 yr.	2.90	0.695	5 yr.	2.25	0.303
6 yr.	3.13	0.705	6 yr.	2.34	0.320
7 yr.	6.56	0.724	7 yr.	3.73	0.345
8 yr.	0.00	0.724	8 yr.	4.44	0.374
9 yr.	0.00	0.724			

cumulative probability of 0.077. From then on, particularly after the third year, the rate declined with the passage of time, but not as sharply as did the rate of discharge. Nine years after discharge the readmission probability was 0.374.

2. *Functional Diagnostic Group.*—Particular attention was paid to the functional or psychogenic psychoses (predominantly schizophrenia, manic-depressive psychosis, and involutional melancholia). Combined as a group, they constituted 49.6% of all diagnoses.

Because of their similarity to those for the total sample, these probabilities are not presented in detailed tabular form, but are merely summarized below.

(*a*) Discharge: Composed almost entirely of certified patients, for whom probation before discharge was practically inevitable, this segment had a probability of discharge during the first six months after admission (0.061) which was even lower than that for the total sample. This enforced initial lag had been overcome by the end of the year, however, at which point the probability had reached 0.476. From then on it remained slightly higher than that for the total sample, attaining 10 years after admission a level of 0.799.

(*b*) Readmission: The probability of readmission at every point during the nine years following discharge was almost identical with that for the total sample. Levels at one, two, and nine years were 0.110, 0.183, and 0.355, respectively.

B. The Variables Studied—Their Effect upon Probabilities of Discharge and Readmission

When derived for sample segments characterized by each of the variables studied, probabilities both of discharge and of readmission displayed essentially the time trends of the total sample probabilities which have already been described. Pointless redundance will therefore be avoided by reporting comparative probabilities pertaining to only two points in time during the follow-up period: discharge probabilities 2 and 10 years after admission; readmission probabilities 2 and 9 years after discharge. In this way both the early and the long-term effect of the variables can be observed.

In the tables of results, the number of cases involved in the derivation of each probability is shown. It can be seen that with some variables the sample was depleted by "unknowns."

Certain categories contained so few cases that probabilities could not be derived. In one instance (readmission by birthplace), sample size in two categories permitted the calculation of total, but not cumulative, nine-year probabilities.

TABLE 2.—*Discharge Probabilities Two Years and Ten Years After Admission and/or Readmission Probabilities Two Years and Nine Years After Discharge, by Social Variables*

Variable	Discharge Probabilities			Readmission Probabilities		
	N	2 Yr.	10 Yr.	N	2 Yr.	9 Yr.
1. *Age						
15-44	80	0.628	0.712	54	0.148	0.415
45-64	80	0.698	0.793	54	0.185	0.342
65+	80	0.414	0.778	22	0.136	0.338
2. Sex						
Males	120	0.626	0.782	71	0.183	0.381
Females	120	0.500	0.667	59	0.136	0.365
3. Environment						
(a) †Total sample						
Rural	120	0.618	0.756	67	0.209	0.478
Urban	120	0.597	0.694	63	0.111	0.266
(b) Total sample by sex						
Male Rural				38	0.184	0.459
Urban				33	0.182	0.290
Female†‡ Rural				29	0.241	0.500
Urban				30	0.033	0.233
(c) †Functional Group						
Rural				43	0.256	0.462
Urban				39	0.103	0.230
4. Marital status						
(a) *Total sample						
Married	120	0.692	0.765	67	0.164	0.392
Not married	120	0.528	0.684	63	0.159	0.355
(b) Total sample by sex						
Male Married	60	0.653	0.735			
Not married	60	0.580	0.794			
Female*§ Married	60	0.725	0.791			
Not married	60	0.467	0.558			
(c) *§Functional group						
Married	54	0.778	0.861			
Not married	65	0.607	0.748			
(d) Total sample by dependency and living situation						
In family						
Dependent Married	22	0.550	0.550			
Not married	45	0.523	0.629			
Independent Married	98	0.711	0.804			
Not married	45	0.660	0.768			
Not in family						
Dependent Married	0	----	----			
Not married	12	0.333	0.333			
Independent Married	0	----	----			
Not married	18	0.306	0.671			
5. Birthplace (Ages 15-64 only)						
Canada	130	0.678	0.754	88	----	0.557
U.K. and U.S.A.	17	0.665	0.799	12	----	0.500
Other	12	0.500	0.682	8	----	0.667
6. Broken home (Ages 15-64 only)						
Yes	34	0.623	0.693	22	0.227	0.365
No	120	0.674	0.773	83	0.145	0.372
7. ‡Education (Ages 15-64 only)						
Grade 8 or less	115	0.645	0.745	59	0.220	0.345
Over Grade 8	42	0.701	0.758	30	0.067	0.457
8. Occupation (All ages, males only)						
Skilled	25	0.653	0.792	13	0.231	0.487
Unskilled	44	0.625	0.732	28	0.250	0.412
Farmers	41	0.618	0.830	24	0.125	0.362

* Statistically significant influence ($P < 0.05$) of the variable on discharge at 2 years.
† Statistically significant influence at 9 years.
‡ Statistically significant influence ($P < 0.05$) of the variable on readmission at 2 years.
§ Statistically significant influence at 10 years.

1. *The Four Variables by Which the Sample Was Stratified* (Table 2).—(*a*) Age: For patients 65 years of age and over, the discharge probability two years after admission (0.414) was much lower than that for patients of ages 15-44 (0.628) and 45-64 (0.698). But while elderly patients left hospital less rapidly, their ultimate

chance of discharge, if they lived, was surprisingly good. Ten years after admission, discharge probabilities at ages 15-44, 45-64, and 65+ were 0.712, 0.793, and 0.778, respectively.

Comparisons of age-specific readmission probabilities were made with reservation. In calculation of the rates from which readmission probabilities were derived, lack of information to the contrary made it necessary to assume that the population at risk had not been depleted by deaths occurring after discharge. The resulting error, while probably fairly constant within each broad age group, was undoubtedly particularly operative at ages 65 and over.

Because of this, all that could safely be concluded from age-specific comparisons was that the probability of readmission was at least as great at ages 65 and over as at the younger ages.

(*b*) Sex: A tendency for the male discharge probability to exceed the female increased with time spent in hospital, until at 10 years the male advantage over the female (0.782 *vs.* 0.667) approached, but did not attain, statistical significance.

The sexes differed little in their probability of readmission. Two years after discharge, the probability for males was 0.183 and that for females was 0.136—a nonsignificant discrepancy that had almost disappeared seven years later.

(*c*) Environment: Two years after admission, rural and urban discharge probabilities were almost identical; eight years later, the rural probability (0.756) barely exceeded the urban (0.694).

Type of environment did, however, affect the probability of readmission. The rural probability was almost twice as great as the urban two years after discharge, and again seven years later, when the difference between their probabilities of 0.478 and 0.266 was statistically significant.

The greater rural readmission probability, which pertained to the functional group as well as to the total sample, was more a characteristic of females than of males. Two years after discharge, male environment-specific probabilities did not differ at all, and, while a rural excess had resulted seven years later, only the larger difference for females (0.500 *vs.* 0.233) proved statistically significant.

(*d*) Marital Status: Being married rather than not married (single, widowed, divorced, or separated) influenced the earliness of discharge more than its eventual likelihood. Two years after admission, the married group's probability (0.692) exceeded the not-married group's (0.528) to a statistically significant degree. Eight years later, however, the married group's advantage had diminished.

The effect of marital status on discharge was even more marked for the functional group than for the total sample, extending, in fact, through to the 10th year after admission. Like that of environment on readmission, the effect was particularly evident among females, for whom, with all diagnoses combined, probabilities by marital status differed significantly both at the 2d year (0.725 *vs.* 0.467) and at the 10th (0.791 *vs.* 0.558).

More detailed analyses suggested that discharge differentials by marital status arose because the married were oftener financially independent and lived, before admission, in a family setting—two circumstances which appeared to favor discharge. The difference in discharge probability between Married and Not Married (both sexes combined) was virtually eliminated by an analysis which allowed for the married group's advantage with respect to these variables.

From discharge on, marital status had no effect on the probability of readmission.

2. *Other Social Variables Studied* (Table 2).—The sample having been subdivided according to the following variables, the influence of age was no longer controlled through stratification. Because of this, with one exception, probabilities were limited to ages 15-64. Those for Occupation apply to males of all ages, but since only the actively employed were involved, the upper age group was lightly represented.

(*a*) Birthplace; (*b*) Broken Home: There was a slight, and far from statistically significant, tendency for the probability of discharge to be lowered, and that of readmission raised, by foreign origin exclusive of the United States and British Isles, and by a broken-home background.

(*c*) Education: Educational attainment did not in any way influence the probability of discharge, but its effect upon early readmission was marked. Two years after discharge, the probability of readmission for those with Grade 8 attainment or less (0.220) was significantly in excess of that for the educationally more advanced group (0.067).

This effect did not pertain to eventual readmission, however. For, in spite of its initial lag, nine years after discharge the probability for the more-educated segment (0.457) was somewhat greater than that for discharges with limited schooling (0.345).

(*d*) Occupation: Male probabilities of discharge and readmission differed little

TABLE 3.—*Discharge Probabilities Two Years and Ten Years After Admission and/or Readmission Probabilities Two Years and Nine Years After Discharge by Hospitalization Variables*

Variables	Discharge Probabilities			Readmission Probabilities		
	N	2 Yr.	10 Yr.	N	2 Yr.	9 Yr.
1. *†Type of admission						
Certified	200	0.577	0.691	90	0.162	0.360
Voluntary	17	0.931	1.000	16	0.063	0.598
Remand	23	0.535	0.690	15	0.267	0.476
2. ‡Duration of symptoms (functional only)						
Under 6 mo.	43	0.823	0.855	32	0.219	0.358
6 mo. to under 2 yr.	24	0.690	0.859	19	0.105	0.165
2 yr. and over	41	0.574	0.729	26	0.192	0.495
3. Time in hospital						
(*a*) Total sample						
Under 1 yr.				86	0.159	0.305
1 yr. to under 2 yr.				29	0.074	0.370
2 years and over				15	0.200	0.429
(*b*) Total sample by age						
15-44 Under 1 yr.				39	0.111	0.306
1 yr. to under 2 yr.				9	0.111	0.444
2 yr. and over				6	0.333	0.778
45-64 Under 1 yr.				35	0.205	0.294
1 yr. to under 2 yr.				14	0.214	0.236
2 yr. and over				5	0.000	0.000
65+ Under 1 yr.				12	0.167	0.333
1 yr. to under 2 yr.				6	0.000	0.333
2 yr. and over				4	0.250	0.25
(*c*) Functional group						
Under 1 yr.				50	0.200	0.280
1 yr. and over				32	0.156	0.408
4. Condition on discharge						
(*a*) Total sample						
Recovered				45	0.133	0.355
Improved				68	0.197	0.417
Unimproved				12	0.167	0.500
(*b*) Functional group						
Recovered				35	0.172	0.382
Improved				40	0.200	0.388
Unimproved				3	----	----
5. *†Specific treatment (functional, ages 15-64)						
Treatment	35	0.558	0.676	23	0.174	0.455
No treatment	62	0.751	0.859	49	0.204	0.337
6. Physical illness in hospital						
Total sample by age						
*†15-64 Ill	29	0.397	0.397			
Not ill	111	0.785	0.879			
*65+ Ill	20	0.214	0.738			
Not ill	19	0.789	0.930			

* Statistically significant influence ($P < 0.05$) of the variable on discharge at 2 years.
† Statistically signifi ant influence at 10 years.
‡ Statistically significant influence ($P < 0.05$) of the variable on readmission at 9 years.

among the following occupational categories: skilled (including all jobs requiring more than rudimentary training, as well as all business, managerial, and professional positions); unskilled; farmers.

Ten years after admission, the discharge probability ranged only from 0.732, for the unskilled, through 0.792, for the skilled, to 0.830 for the farmers. At the end of the second year, occupation-specific probabilities were almost identical.

Nine years after discharge, the readmission probability was 0.362 for the farmers, 0.412 for the unskilled, and 0.487 for the skilled, indicating a trend which fell short of statistical significance,

3. *Variables Related to Hospitalization* (Table 3).—(*a*) Type of Admission: The probability of discharge for voluntary admissions, both at 2 years (0.931) and at 10 (1.000), exceeded, to a statistically significant degree, those for certified and remanded admissions.

Readmission was also more probable for the voluntary group, but not significantly so. Certified patients fared best with respect to readmission, but nine years after discharge their advantage over remanded admissions (0.360 *vs.* 0.476) was not outstanding.

(*b*) Duration of Symptoms Before Admission: To avoid distortion by long-standing cases of mental deficiency, senile deterioration, and other nonpsychogenic conditions, comparisons by duration of symptoms were limited to the functional diagnostic group.

Two years after admission, discharge probabilities by duration of under six months, six months to two years, and two years and over were 0.823, 0.690, and 0.574, respectively, suggesting that early hospitalization had an accelerating effect upon discharge. However, eventual discharge was much less influenced by this factor, as evidenced by the corresponding 10-year probabilities of 0.855, 0.859, and 0.729.

Those first admitted less than two years, but more than six months, after the onset of symptoms seemed to have the best chance of remaining out of hospital after discharge. Those admitted with symptoms of at least two years' standing were significantly more likely to return within nine years, while admission with symptoms of less than six months' duration was associated with an intermediate readmission probability.

(*c*) Time in Hospital: The probability of eventual readmission tended to mount with increasing time spent in hospital before discharge. But even within the functional diagnostic group, where it was most evident, the trend lacked statistical significance. Moreover, early readmission (within two years after discharge) seemed least likely when at least one year, but less than two, had been spent in hospital. Finally, analysis by age established that any tendency for long-term hospitalization to increase the probability of readmission was confined to the age group 15-44.

(*d*) Condition on Discharge: Condition on discharge influenced the probability of readmission, but much less than might be expected. Two years after discharge, total sample probabilities for the recovered, improved, and unimproved were 0.133, 0.197, and 0.167, respectively. At the end of the follow-up period these probabilities had risen to 0.355, 0.417, and 0.500, demonstrating only a slight and nonsignificant tendency for discharge without recovery to increase the chance of eventual readmission. No more significant effect was observed when the functional group was analyzed separately.

(*e*) Treatment: This analysis was limited to what was believed to be the most pertinent admission segment: the functional group, ages 15-64.

Patients receiving specific physical treatment (electroshock or insulin therapy) were less likely to leave hospital within a decade than were patients receiving no such treatment. Discharge probabilities for the treated and untreated differed significantly at 2 years (0.558 *vs.* 0.751) and at 10 years (0.676 *vs.* 0.859).

The patient having been discharged, however, the chance of returning to hospital

was not materially influenced by the treatment factor. Nonsignificant differences in readmission probabilities, favoring the treated at two years and the untreated at nine years, could easily be ascribed to chance variation. The likely explanation for these rather startling findings will be discussed.

(*f*) Physical Illness While in Hospital: In this analysis, terminal illnesses were excluded because of their inherent bias toward withdrawal by death.

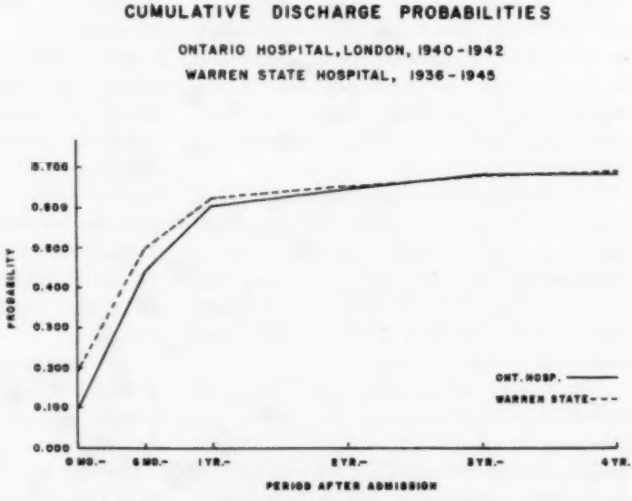
Both at ages 15-64 and 65+, a physical illness while in hospital impeded discharge. At ages 15-64 the effect was marked throughout the follow-up period, as evidenced by probabilities for the physically ill and the physically not ill of 0.397 and 0.785 two years after admission and 0.397 and 0.879 eight years later. The early-discharge discrepancy was even more pronounced at ages 65+, although eventual discharge seemed less severely handicapped by a physical illness.

sample of 240 patients first admitted to the Ontario Hospital, London, during the years 1940 to 1942.

Because release from Warren State Hospital on probation was counted as discharge, while only formal discharge from the London Hospital was considered, discharge probabilities during the first six months after admission could not be legitimately compared. After the first year, when the discrepancy in discharge definitions would be less disrupting, the two probabilities were almost identical.

Comment

The over-all probability levels of discharge and readmission were far from discouraging. Although they pertained to a sample whose identity with its universe was disturbed through stratification, the coincidence of the probability of discharge with that from another study based on total first



Cumulative discharge probabilities (Ontario Hospital, 1940-1942) and Warren State Hospital, Warren, Pa. (1936-1945).

4. *Total Sample Discharge Probability Compared with That at Another Hospital* (Figure).—The reworking of published data [2] permitted comparison of a five-year discharge probability based on all 5263 patients first admitted to Warren State Hospital, Warren, Pa., during the years 1936 to 1945, with that based on the stratified admissions suggested that they were not unduly artificial. The striking similarity between the discharge probabilities at the two hospitals compared is actually worthy of emphasis. Further comparisons might well reveal that, in any one time period, administrative differences among mental hospitals on this continent create less variation in

discharge levels than is sometimes supposed.

Of the factors found to influence the probability of discharge, none appeared more crucial than the mere passage of time after admission. Except at ages 65 and over, failure to leave hospital within two years, in spite of a better than even chance of doing so, made ultimate discharge extremely uncertain. The exception could have been a reflection of a tendency for poor discharge risks among the elderly to be progressively eliminated through death.

Of the social variables examined, the probability of discharge proved to be significantly influenced by marital status, and that of readmission, by rural-urban environment and educational attainment.

The discharge advantage enjoyed by married admissions seemed to be closely associated with the group's propensity for financial independence and close family ties. This suggested that the advantage might have been gained, in part at least, from the availability of better facilities for maintenance, care, and supervision at home—a factor thought to be contributive to the group's favorable first-admission rate.[3]

Comparable elaboration of the basic observation that urban residence and advanced schooling discouraged readmission was precluded by the failure of hospital case histories to provide needed data. Some mention should be made, however, of the apparent reversal in the present results of the usual urban-rural relationship. In first-admission studies by ourselves and others,[3] urban rates have been found to exceed the rural. The reverse tendency of the readmission rates is certainly curious and worthy of further study.

Another point of interest in the comparison between our investigation of readmission and first admission is the greater effect of environment and marital status upon females with readmission, in contrast to their more marked influence upon males with first admission.

Because it was impossible to trace discharges not readmitted, it was not known whether the significant variables influenced the rate of relapse, or simply the rate at which relapsed patients were hospitalized. This predicament, analogous to that which complicates attempts to compare incidence on the basis of first-admission rates, has been considered in another investigation, as yet unpublished.

At least one suggestion of an influence on the readmission probability of a varying demand for hospitalization did, in fact, appear. The prevalent belief that early psychiatric treatment encourages a permanent cure was in some measure substantiated by the fact that those first admitted with symptoms of intermediate duration enjoyed a significant nonreadmission advantage over those first admitted with symptoms of long duration. Failure of those first admitted with symptoms of short duration to enjoy an even greater advantage could have reflected a particular pressure for hospitalization conducive both to early first admission and to ready readmission.

While not proved, it was suspected that at least some of the variables affected probability differentials indirectly, through a process of selection, rather than through any direct influence. Selection on the basis of diagnostic composition probably enhanced the voluntary admission group's favorable discharge outlook. Physical illness may to some extent have resulted from, rather than have contributed to, poor prognosis, since accidents, usually the result of acutely disturbed behavior, figured prominently among the physically ill who were not discharged. The favored position of the untreated group almost certainly stemmed from a tendency for physical treatment, in its early days, to have been withheld when rapid, spontaneous recovery seemed assured. The latter observation, incidentally, is a practical example of a fallacy so often stated in theoretical terms—that of studying the efficacy of a treatment procedure without prior unbiased allocation of patients to the treated and untreated groups.

Throughout the presentation of results, distinctions were made as to whether the influence of significant discharge and readmission variables was upon the early or long-term probabilities. On the basis of when during the follow-up period statistical significance pertained, it seemed that age, marital status, and physical illness at ages 65+ influenced early discharge more than its eventual outcome, while type of admission, treatment, and physical illness at ages 15-64 exerted an influence throughout the entire follow-up period. On the same basis, it appeared that the effect of education was limited to early readmission, while that of rural-urban environment and duration of symptoms pertained more to eventual readmission. Here was yet another observation in need of more intensive investigation before an interpretation could be attached.

In short, this study indicated the range and complexity of factors influencing discharge and readmission probabilities. But it also proved that these factors cannot be adequately assessed through use of case-history data obtained in retrospect. It is for this reason that plans are being laid to follow a large sample of patients on an intimate, forward basis.

Summary

Probabilities of discharge and readmission were derived for a cohort of 240 patients followed in retrospect for 10 years after their first admission to a mental hospital during the years 1940 to 1942.

The probability of discharge was found to be favorably influenced, to a statistically significant degree, by admission before age 65, married status, voluntary admission, and freedom from physical illness while in hospital. The probability of not being readmitted was favorably influenced by admission from an urban environment, by education beyond the elementary level, and by having been first admitted with symptoms of intermediate rather than of long duration.

It is hoped that these and other more tentative leads may be pursued through a more ambitious follow-up study done on a prospective basis.

APPENDIX

Method Used to Calculate Discharge and Readmission Probabilities

A. Discharge Probability (Table 4)

The discharge rate for a specific interval of time after admission (R_x) is the ratio of discharges during the period (a_x) to the

TABLE 4.—*Calculation of Cumulative Discharge Probabilities*
Total Sample, 240 Admissions

Period After Admission x	Number Entering Period l_x	Discharges During Period a_x	Withdrawals (Deaths) During Period d_x	Number Exposed $l_x - \frac{1}{2}d_x$ $= N_x$	Discharge Rate Per 100 $\frac{a_x}{N_x} \times 100$ $= R_x$	Cohort L_x	Cohort Discharges $R_x \times \frac{L_x}{100}$ $= A_x$	Cumulative Proportion Discharged (Probability) P
0 mo.	240	9	21	229.5	3.92	1000.0	39.2	0.039
1 mo.	210	4	7	206.5	1.94	960.8	18.6	0.058
2 mo.	199	0	5	196.5	0.00	942.2	0.0	0.058
3 mo.	194	0	2	193.0	0.00	942.2	0.0	0.058
4 mo.	192	3	3	190.5	1.57	942.2	14.8	0.073
5 mo.	186	4	0	186.0	2.15	927.4	19.9	0.093
6 mo.	182	7	4	180.0	3.89	907.5	35.3	0.128
7 mo.	171	14	3	169.5	8.26	872.2	72.0	0.200
8 mo.	154	10	0	154.0	6.49	800.2	51.9	0.252
9 mo.	144	20	2	143.0	13.99	748.3	104.7	0.356
10 mo.	122	8	2	121.0	6.61	643.6	42.5	0.399
11 mo.	112	7	1	111.5	6.28	601.1	37.7	0.437
1 yr. 0 mo.	104	20	9	99.5	20.10	563.4	113.2	0.550
1 yr. 6 mo.	75	9	4	73.0	12.33	450.2	55.5	0.605
2 yr. 0 mo.	62	3	6	59.0	5.08	394.7	20.1	0.625
2 yr. 6 mo.	53	3	1	52.5	5.71	374.6	21.4	0.647
3 yr.	49	4	6	46.0	8.70	353.2	30.7	0.678
4 yr.	39	1	2	38.0	2.63	322.5	8.5	0.686
5 yr.	36	1	3	34.5	2.90	314.0	9.1	0.695
6 yr.	32	1	0	32.0	3.13	304.9	9.5	0.705
7 yr.	31	2	1	30.5	6.56	295.4	19.4	0.724
8 yr.	28	0	1	27.5	0.00	276.0	0.0	0.724
9 yr.	27	0	2	26.0	0.00	276.0	0.0	0.724
10 yr.	25					276.0		

exposed population (N_x), expressed per 100.

The population exposed is estimated by subtracting from the number in hospital at the beginning of the interval (l_x) one-half the number of deaths during the interval (d_x). In so doing, it is assumed that deaths are distributed more or less evenly throughout an interval, so that those who die are exposed, on the average, for half an interval.

The rates at successive intervals are applied, in turn, to a hypothetical cohort (L_x) which begins at 1000 and which is then progressively depleted by discharge.

The resulting number of discharges at each interval (A_x) is the number from the original 1000 that would have been discharged, on the basis of the observed rates, if withdrawal from exposure through death had not been operative at that or preceding intervals.

When these discharges are cumulated and expressed as a proportion of the starting cohort (P), they represent the probability of discharge up to, and including, period x, if exposure to discharge is sustained for that time.

B. Readmission Probability

The procedure is the same as that for discharge after three substitutions are made in the entries:

1. Column x becomes Period after Discharge
2. Column a_x becomes Readmissions During Period
3. Column d_x becomes Withdrawals During Period, resulting from patients having reached the end of the 10-year period of observation following admission.

Method Used to Test for Statistical Significance

To determine whether or not observed probability differentials were statistically significant, use was made of the conventional standard error of the difference between two proportions. To do this, estimates were made of "effective sample size," using a method described by Cutler [4] to give the equivalent sample size in which there are no withdrawals, but which yields the same probability and the same number of discharges or readmissions as were observed. Effective sample size is computed as

$$ESS = \frac{d_x}{Cum\ P_x}$$

where

d_x=sum of the number of persons known to have been discharged or readmitted through interval x.

$Cum\ P_x$=cumulative proportion discharged or readmitted through interval x.

REFERENCES

1. Canada, Dominion Bureau of Statistics, Mental Health Statistics, 1954, Ottawa, Ont., Queen's Printer and Controller of Stationery, 1955.

2. Kramer, M.; Goldstein, H.; Israel, R. H., and Johnson, N. A.: A Historical Study of the Disposition of First Admissions to a State Mental Hospital, Public Health Service Publication 445, U. S. Department of Health, Education, and Welfare, Public Health Service, National Institute of Mental Health, 1955.

3. Wanklin, J. M.; Fleming, D. F.; Buck, C. W., and Hobbs, G. E.: Factors Influencing the Rate of First Admission to Mental Hospital, J. Nerv. & Ment. Dis. 121:103, 1955.

4. Cutler, S. J.: Cancer Illness Among Residents in Atlanta, Georgia, 1947, Cancer Morbidity Series 1, Bethesda, Md., National Cancer Institute, 1950.

Physiologic Stress Response Evaluation by Focused Interviewing

Capt. SANFORD I. COHEN
Capt. ALBERT J. SILVERMAN
and
Capt. GEORGE ZUIDEMA (MC), U. S. A. F.

Introduction

The use of broad, scanning research tools which attempt to correlate multiple psychologic and physiologic factors often disguises relationships which might be discernible by techniques intended to investigate specific links in a psychophysiologic chain of events. This paper will describe a preliminary attempt to utilize focused interviews as part of a psychophysiologic battery to evaluate the responses of subjects to controlled stresses. We attempted to direct our efforts at evaluating specific affective states which might influence the subject's somatic stress responses. To do this, it was necessary to identify the physiologic changes possible when persons were exposed to various stressful situations, and then theorize on the psychodynamic factors which might be causally related to physiologic and biochemical variations influencing the subject's response.

The problem to be investigated in this project was the relationship of emotional factors to tolerance to g forces. Pilots in high-speed aircraft and subjects on the human centrifuge show marked inter- and intraindividual variations in their black-out levels which cannot be accounted for on a physiologic basis. Exposure to g forces causes the centrifuging of blood away from the upper extremities, head, and eyes and may result in decreased peripheral vision, complete black-out, and unconsciousness. Physiologic compensatory mechanisms attempt to maintain the blood pressure and probably are dependent on carotid sinus reflexes, autonomic nerve tone, neurohormonal substances, and the reactivity of the vascular bed. The fact that the maintenance of blood pressure was involved in the tolerance to g force led us to speculate that the influence of emotional factors in g tolerance was due to its ability to influence blood pressure levels.

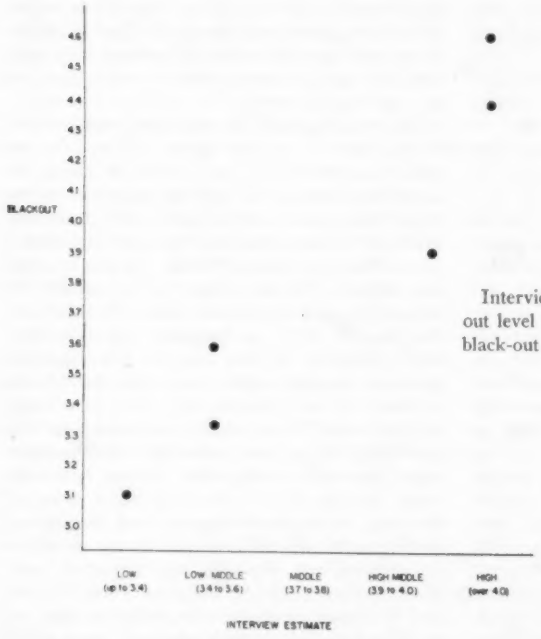
Considerable research has indicated that the handling of aggressive impulses is involved in the development of hypertension, poorly suppressed or repressed hostility being associated with hypertensive effects.[1] Funkenstein's[2] work has suggested that the outward expression of anger in experimental and life situations was accompanied by blood pressure elevation and the excessive secretion of arterenol-like substances. On the other hand, anger directed inward, or anxiety, was associated with hypotensive responses and an excess secretion of adrenaline-like substances. Von Euler[3] described the release of adrenaline with emotionally provoking stimuli, particularly when anxiety was aroused, but felt that arterenol was released in response to vascular shifts requiring compensatory blood pressure elevations. Finally, recent work by Goodall and Meehan * suggests that persons demonstrating high g tolerances on a particular day put out more arterenol than subjects with low g tolerances during the exposure period.

Hence it was felt that subjects displaying

Received for publication June 21, 1956.

Stress and Fatigue Section and Acceleration Section, Aero Medical Laboratory, Wright-Patterson Air Force Base, Dayton, Ohio.

* Goodall, McC., Jr., and Meehan, J. P.: Correlation of g Tolerance with Urinary Adrenaline and Nor-Adrenaline, to be published.



Interviewers' estimate of the subjects' black-out level compared with the actual g level at which black-out occurred.

high levels of anxiety would tend to have low g tolerances, while those who demonstrated aggressivity and low levels on anxiety would have high g levels. It was felt that these affects and impulses were significant emotional determinants influencing some of the cardiovascular mechanisms responsible for variations in g tolerance. Preliminary work partially tested and confirmed this hypothesis by the use of focused projective techniques.†

Another part of the research effort directed at evaluating this would be the use of interviews aimed at evaluating the subject's anxiety and the arousal, and handling, of aggression during the testing procedure.

† Cohen, S. I.; Silverman, A. J., and Zuidema, G.: Psychophysiologic Integration in the Prediction of Physiologic Stress Tolerance from Projective Test Stories, presented at the Rocky Mountain Psychological Association, June 11-13, 1956. Silverman, A. J.; Cohen, S. I., and Zuidema, G.: Prediction of Stress Tolerance from Projective Test Stories, presented at the American Psychological Association, Chicago, Aug. 30-Sept. 5, 1956. Reference 4.

Methodology

The human centrifuge was used as the physiologic stresser. With it subjects could be exposed to controlled increments in g stress and their tolerance for that day evaluated, using black-out as an end-point. Hence graded cardiovascular stress could be imposed on subjects and their physiologic changes closely observed.

Six subjects were centrifuged to establish their black-out levels on a particular day.

Just prior to beginning the ride, after the subjects were seated and various bivelectric instruments were connected, the subjects were chastised for moving about in the cab. They were told to stop obstructing the experiment. This was done at a time when the subject's bioelectric records showed no movement (they were also being observed on a closed-circuit TV screen). This verbal stimulus had a twofold purpose: 1. The first was to produce in the subject an affective response. Being volunteers, it was anticipated that some might resent the curt manner in which the chastisement was presented. However, with others it was felt there would be anxiety over failure to perform adequately in a way which was expected. 2. Of more importance, however, was the utilization of this verbal stimulus as a focus for interviews the subjects would have following their g runs.

Immediately after the runs the subjects were

interviewed, and the interview was recorded. The object was to attempt to evaluate the degree of the aggressive feelings present and the manner in which they were handled, as well as the level of anxiety. The technique used was first to elicit the subject's spontaneous description of "how he felt" and the factors influencing his feelings. The level of affective arousal was determined by the diffuseness of his response. That is, if the subject was aroused to the point of panic, it would be anticipated that all events would be interpreted as threatening or anxiety-provoking. On the other hand, the less anxious the person, the more able he would be to associate various feelings to specific and appropriate situations. An attempt was made to evaluate whether the primary affect experienced was anger or anxiety. The interviewer tried to keep his evaluation to the two areas mentioned, anger and/or anxiety, and to evaluate in addition whether these were related, e. g., the arousal of anger, producing anxiety, or whether they were unrelated, e. g., anxiety about the ride and anger at the stimulus. Associations were sought only in relation to various aspects of the testing situation to clarify the meaning of events to the subject, and to determine from his associations the aggressive or anxiety-provoking connotations of the test situation. After a spontaneous account of his feelings, the subject was asked whether these were things which were unpleasant, and later, more specifically, the events which made him anxious or irritated. The chastising stimulus would not be mentioned specifically by the interviewer until the subject felt he had completely described his feelings. If the subject did not mention the stimulus in the spontaneous account of his feelings, or after the interviewer had repeated several times, "Were there any events which made you anxious or irritated?" The subject was asked specifically about his reaction to the statement. Thus an attempt was made to evaluate the degree of anxiety and arousal of aggressive impulses by judging the subject's spontaneous verbalizations and associations, his response to maneuvers intended to get him to focus on specific events by mentioning specific affects, and, lastly, by focusing on his response to a chastising statement. The g tolerance was considered low if the primary affect of the subject appeared to be intense anxiety, regardless of the source of the anxiety, and if other feelings were masked and inconsequential in the face of the high level of apprehension. The anxiety might emanate from pre-run fears, the affect stimulus, the rides themselves, or some preceding event. On the other hand, subjects who demonstrated little overt anxiety and who were able to associate it with appropriate and specific events, and who, in addition, described aggressive impulses, were placed on the high side of the scale. To be scored in the high group itself, the subjects had to demonstrate that, although affect was aroused, they were able to master it satisfactorily by some appropriate defense or activity.

The handling of the stimulus statement was felt to be a function of the degree of arousal of the subject at the time it was made or during the ride—the meaning of such a statement to the subject, in terms of his personality structure, based on his past associations and his usual method of handling psychologic threats. Finally, if anger was present, the subject's ability to deal with his aggressive impulses was evaluated. This included the subject's ability to discharge aggressive feelings adequately. It was felt this was associated with the subject's ability to master the stresses imposed on him, whether they were psychologic or physiologic. For example, if the centrifuge ride was described as pleasurable by subjects whose anger had been aroused, then this was tentatively taken to mean, in part, that they had a means of discharge of aggressive impulses, and the meaning of the centrifuge ride, as well as the sensations experienced, was explored. On the other hand, the centrifuge might be conceived of as a threat and be anxiety-provoking enough that it could not be utilized as a channel for release of anger which may have been aroused.

The interviewer (who had no knowledge of the g tolerance) recorded his impression of the affective state of the subject, and estimated the g tolerance of the day.

Results

The interviewer estimated the subject's g tolerances according to the following categories: High, High Middle, Middle, Low Middle, and Low. The ranges for each class were as follows:

High g tolerance, over 4 g exposure before black-out
High Middle, 3.9-4.0 g
Middle, 3.7-3.8 g
Low Middle, 3.4-3.6 g
Low, below 3.4 g

The figure shows the investigators' estimates on the abscissas and the actual g tolerance on the ordinates.

Five of the six subjects were correctly placed in one of the above five classes. One subject was classified as Low Middle (3.4-3.6), whereas his actual g tolerance was 3.3.

The following records are summaries of examples of subjects in each class:

SUBJECT 1.—The subject described overt feelings of anxiety spontaneously, which occurred just prior to the ride and during it. He said "he had never experienced any feeling like the tachycardia and uneasiness he felt during the ride." He was unable to attribute his apprehension to any specific event and, when pressed, was not able to mention specifically any "significant occurrences" which might have contributed. He did not mention the affect stimulus, and, when it was recalled for him, he said it did irritate him mildly but he was so scared he forgot it, and besides "he figured he probably was moving." He also expressed self-recrimination for "ruining the experiment" by blacking-out so early. He expressed multiple concerns about physical sensations during the interviews and was markedly anxious throughout.

Impression—Marked anxiety, diffuse and free-floating. His g tolerance was graded by the interviewer as Low. (Actual g tolerance for that day was 3.1.)

SUBJECT 2.—The subject began the interview by spontaneously denying feeling as apprehensive as in previous runs, feeling "consciously" relaxed, and "almost finding the ride pleasurable." He did express irritation at nonhuman elements of the experiment, but only with marked urging did he cautiously express mild irritation at some of the people running the experiment. The stimulus had to be mentioned, and he gave a mixed response, at first blaming himself for moving, although he was "not conscious of it," and then expressing irritation over being chastised so curtly. However, he then described feeling fearful that the experiment would be repeated if he did not cooperate (punishment). He described feeling helpless during the rides, as if the centrifuge were going to throw him out and he had to defend himself from attack. Furthermore, he felt this ride was a challenge in that he had the feeling the laboratory personnel considered him a low-g subject, and this irritated him. He felt he would try and prove they were wrong by "beating the machine."

Impression.—Although this subject displayed moderate anxiety with concerns of bodily injury and loss of status, the anxiety did not appear overwhelming or free-floating in that he could relate it to specific events and ideas, although some of these were not completely reality-based. On the other hand, he did express some aggressive hostile feelings; however, these aroused fears of punishment, and were handled in part by a turning inward of the anger, and in part by displacing it to the "machine." The primary affect was felt to be anxiety, but not to an overwhelming degree. Secondary feelings of anger with aggressive wishes were present, which were handled with some difficulty.

His g level was estimated to be Low Middle. (Actual g tolerance was 3.6.)

SUBJECT 3.—This subject spontaneously related feeling moderately apprehensive at the beginning of the ride and related it to specific effects of the test procedure (with which she was unfamiliar). However, she said this feeling was dissipated after she was able to evaluate certain aspects of the test (and felt she could master the situation). She spontaneously described being annoyed at various delays in the experiment but did not mention the stimulus until specific events were asked for by the interviewer. She then stated she thought it was part of the experiment situation, and felt a little annoyed at its being used. She realized she had not moved, but did not respond to the statement because she did "not feel it necessary" (to demonstrate her control of the situation). She felt quite relaxed during the rides, and felt she "could handle the centrifuge," being familiar with this experience. She felt that the experiment was aimed at provoking black-out, but that the stimulus statement had no effect on her tolerance.

Impression.—This subject was able to master the stresses of the experiment. Her primary affect was anger with aggressive, hostile impulses, dealt with by "defeating the experimenters" and thus, in a socially acceptable way, expressing the anger directly at the irritating source. Her anxiety was minimal, related to specific events and ameliorated after she felt in control.

Her g tolerance was estimated as high. (Actual tolerance was 4.6.)

Comment

The use of interviews to evaluate specific affective constellations in subjects in a circumscribed situation was successful in a small group of subjects in predicting their physiologic responses when exposed to cardiovascular stress. Physiologic patterns may not correlate as closely with personality structure or specific ideational content, and may account for the lack of specificity in psychosomatic research in many areas. It seems plausible to assume that the affective state at any one moment in time is closely

related to neurophysiologic events in the limbic structures, and perhaps associated with characteristic and localized hypothalamic responses.

We worked from the assumption that the influence of emotion on g tolerance was mediated through the effects of affective states on blood pressure, anxiety being related to vasodilation, and anger and aggression, to vasoconstriction, on the basis of differential adrenaline-arterenol ratios, this differential ratio possibly being related to selective stimulation of specific hypothalamic centers.

Further work is being done to evaluate the neurophysiologic, cardiovascular, and biochemical correlates of various affect states, as judged by interviews and projective tests, and will be reported at a later date.

Summary

Preliminary studies on a small group of subjects suggest that focused-interview techniques, directed at evaluating the affective constellations of the subjects, is a promising method of judging cardiovascular responses to a physiologic stresser. The conceptual framework involved the integration of specific affect states, i. e., anger or anxiety, adrenaline-arterenol ratios, and related blood pressure patterns.

Box 8508, Area B.

REFERENCES

1. Wittkower, E. D., and Cleghorn, R. A.: Recent Developments in Psychosomatic Medicine, Philadelphia, J. B. Lippincott Company, 1955, pp. 300-320.

2. Funkenstein, D. H.; King, S. H., and Drolett, M.: Direction of Anger During a Laboratory Stress Inducing Situation, Psychosomatic Med. 16:404 (Sept.-Oct.) 1954.

3. Von Euler, U. S.: Nor-Adrenaline in Hypotensive States and Shock, Lancet 2:151-154 (July 23) 1955.

4. Silverman, A. J.; Cohen, S. I., and Zuidema, G.: Psycho-Physiologic Investigations in Cardio-Vascular Stress, Am. J. Psychiat., to be published.

Chlorpromazine and Hepatic Function

VERNON KINROSS-WRIGHT, M.D.
and
JOHN H. MOYER, M.D., Houston, Texas

Chlorpromazine * has been used with great success in all fields of medicine and surgery in treating neuroses, psychoses, nausea, and vomiting and as an agent to augment the effect of anesthetics and opiates. One of the side-effects observed with the use of the drug is an obstructive type of jaundice that may develop insidiously or with an abrupt onset of mild grippe-like symptoms. The duration of the jaundice is variable, and its onset seems to be related to the duration of treatment.

The precise determination of the incidence of this type of jaundice has been difficult. Obviously, some cases have not been reported. An estimate of the incidence, based on reports in the American, Canadian, and British literature, has been published.[1] Although the average incidence is about 1.4%, Table 1 indicates a wide variation in the incidence of jaundice reported for individual studies. In the authors' experience, which includes more than 3000 patients, the incidence is less than 0.1% despite the use of intensive dosage regimens.

The following study was undertaken to determine whether results of liver function tests could be used to predict the development of jaundice. If changes in liver function can be detected before the appearance of jaundice, it might be possible to avoid this troublesome side-effect by discontinuing the drug during the incipient stage of hepatic dysfunction. However, if changes in liver function do not occur before the onset of jaundice, then the use of routine liver function tests during the administration of chlorpromazine is of little value.

Received for publication May 11, 1956.

Department of Psychiatry and Pharmacology, Baylor University College of Medicine.

* Generic name for Thorazine, supplied by Smith, Kline & French Laboratories, Philadelphia.

TABLE 1.—*Incidence of Jaundice in Psychiatric Patients on High-Dose, Long-Term Therapy* *

Investigator (Senior Author)	Number of Patients Treated	Number of Patients Jaundiced	Percentage of Patients Jaundiced
Cohen (U.S.)	1000	6	0.6
Goldman (U.S.)	900	2	0.2
Lomas (Brit.)	800	11	1.4
Bird (U.S.)	750	13	1.7
Pollack (U.S.)	500	20	4.0
Prokopowycz (U.S.)	520	3	0.6
Sainz (U.S.)	336	1	0.3
Lehmann (Can.)	283	8	2.8
Freyhan (U.S.)	250	1	0.4
Willner (U.S.)	240	1	0.4
Vaughan (Brit.)	224	3	1.3
Coats (U.S.)	190	5	2.6
Ostrow (U.S.)	182	5	2.8
Ford (U.S.)	149	1	0.7
Litteral (U.S.)	125	3	2.4
Ayd (U.S.)	100	3	3.0
Denber	4360†	61	1.4
Total	10,909	157	1.4

* From article by R. B. Doughty (The Incidence of Jaundice Associated with Chlorpromazine Therapy), in "Chlorpromazine and Mental Health," published by Lea E. Feliger, Philadelphia, 1955, p. 196.
† Report on European patients.

Material and Method

Liver function tests were conducted on two groups of patients to determine whether hepatic damage resulted from the administration of chlorpromazine. Thirty medical patients (Group I) were given chlorpromazine in order to study toxic reactions; thirty-three psychiatric patients (Group II) received the drug as part of therapy for their mental illness.

Group I.—Patients in this group were selected from patients hospitalized for a chronic disease not associated with hepatic dysfunction. During their first week of hospitalization patients underwent the following liver function tests: serum alkaline phosphatase, serum bilirubin, thymol turbidity, sulfobromophthalein U. S. P. (Bromsulphalein), cephalin flocculation, and urine urobilinogen determinations. Urinalysis and a complete blood count were done also. Patients with hepatomegaly or laboratory evidence of hepatic disease were dropped from the study.

All patients received 100 mg. of chlorpromazine per day in four divided doses (at meals and bedtime). Fifteen patients received the drug for two to four weeks; fifteen received the drug for five to eight weeks. Liver function tests were repeated

every three days during the administration of chlorpromazine and for two weeks thereafter. A complete blood count and urinalysis were done once a week.

Group II.—Diagnoses of the 33 hospitalized psychiatric patients in this group included schizophrenia, senile dementia, manic-depressive psychosis, and severe psychoneuroses of varied etiology. In addition to their primary psychiatric conditions, five patients had a history of chronic alcoholism. After their admission to the psychiatric ward, all patients underwent the following liver function tests: serum bilirubin, thymol turbidity, sulfobromophthalein, cephalin flocculation, and urine urobilinogen determinations. Urinalysis and blood counts were also done. Results of initial sulfobromophthalein tests of two patients (both with histories of chronic alcoholism) were abnormal. In one of them sulfobromophthalein retention was 24%, in the other 20%; the latter patient also had a 2+ cephalin flocculation test. Both patients had enlarged livers.

During the first week of therapy, patients received chlorpromazine intramuscularly. Usually, 50 mg. of the drug was given four times a day. After a few days of therapy, chlorpromazine was administered orally, and the amount of the drug progressively increased up to a maximum dose in this study of 2000 mg. per day. Treatment was continued for up to three months (Table 2). Liver function tests were repeated on the second day of hospitalization and every four days during the administration of chlorpromazine. A complete blood count and urinalysis were done on each patient each week.

Results

GROUP I.—Of the 30 patients in this group, 15 received 100 mg. of chlorpromazine per day for two to four weeks; 15 received 100 mg. of the drug for one month or more. Results of all liver function tests during the administration of the drug and for two weeks thereafter were within normal limits and did not reflect evidences of hepatic damage. Likewise, urinalyses and blood counts failed to show evidence of renal damage or an alteration in hematopoietic function.

TABLE 2.—*Summary of Dosage Schedules of Chlorpromazine Given to Psychiatric Patients*

Dose, mg. per day	200-500	500-1000	1000-2000
No. of patients treated	33	25	10
Duration of therapy			
Less than 1 wk.	--	6	2
1-2 wk.	--	7	3
2-4 wk.	4	6	4
4-6 wk.	7	5	1
6-8 wk.	7	1	--
8-10 wk.	8	--	--
10-12 wk.	4	--	--
12-14 wk.	3	--	--

GROUP II.—Thirty-three psychiatric patients received varied doses of chlorpromazine for periods of up to three months. Results of liver function tests were not significantly altered during the course of therapy despite large doses of 1000 to 2000 mg. of chlorpromazine per day which were given to 10 patients. Urinalyses and blood counts were normal on all patients. Results of sulfobromophthalein and cephalin flocculation tests of the two patients who gave evidence of hepatic damage at the beginning of the study became normal within four to six weeks, during which time the patients received 200 and 600 mg., respectively, of chlorpromazine per day.

Nature of Jaundice Following Chlorpromazine

It appears that there is a tendency for physicians to withhold chlorpromazine completely, or give it in inadequate amounts, because of a fear of hepatocellular damage. The results of the current study indicate that chlorpromazine does not interfere with hepatic function in any predictable manner detectable by the usual tests of hepatocellular function even when given in massive doses over relatively long periods of time.

The clinical syndrome of jaundice associated with chlorpromazine therapy is variable.† Choluria and acholic stools are seen in most patients; pruritus is seen in about two-thirds of the patients. The mild to moderate hepatomegaly often accompanying infectious hepatitis is not a prominent part of the syndrome. Although eosinophilia is occasionally seen in some patients, the results of other blood studies are usually nor-

† References 2-6.

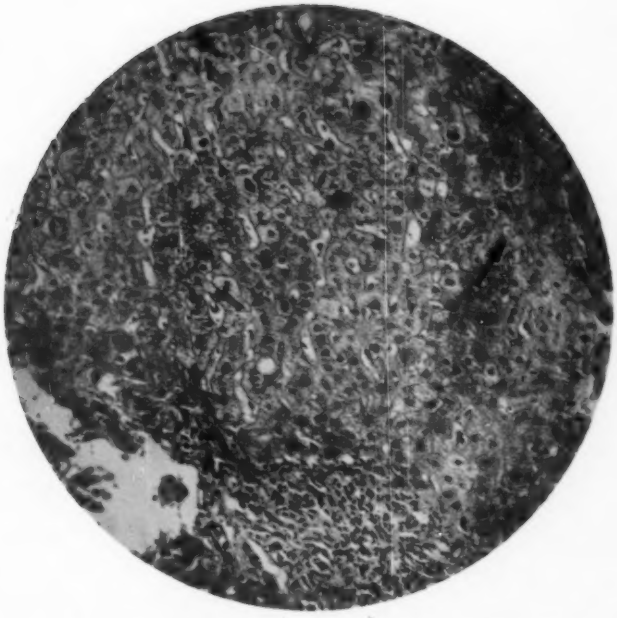


Fig. 1.—Liver biopsy specimen from Patient 2 taken five days after onset of jaundice, showing some lymphocytic infiltration and occasional plugs in the biliary canaliculi (indicated by arrow). Except for vacuolation, the liver cells were normal.

Fig. 2.—Liver biopsy specimen of Patient 2 taken 21 days after onset of jaundice, showing an essentially similar picture. The lymphocytic infiltration is less prominent, but vacuolation of the liver cells is slightly more marked. Arrows indicate distended biliary canaliculi.

mal. Infrequently, mild hypotension, myalgia, diarrhea, dermatitis, lethargy, and slight mental confusion may be part of the clinical picture.

Results of liver function tests done on patients with jaundice related to chlorpromazine therapy are similar to those obtained on patients with extrahepatic obstruction. There is customarily an elevation of the serum alkaline phosphatase and serum cholesterol, with little or no disturbance of the cephalin flocculation and thymol turbidity. Elevated serum alkaline phosphatase tests are rarely associated with damage to the liver parenchyma, and, with a few exceptions, the levels return to normal within a few weeks. Microscopically there is to be found a stasis of bile in the intralobular canaliculi, with or without inflammatory infiltration. When the latter is present, it is mainly lymphocytic.

Although the following two cases of jaundice were not observed in the study being reported on, they did, however, occur at our hospital, and serve to point up the clinical course and findings of jaundice associated with chlorpromazine therapy. Case 1 is atypical of the type of jaundice usually seen. Case 2 represents the commoner clinical course of jaundice and was reported on elsewhere.[7]

Report of Cases

CASE 1.—A 34-year-old white woman became markedly nauseated during the third month of her pregnancy and was placed on 25 mg. of chlorpromazine four times a day. After 10 days of medication she suddenly became jaundiced and developed a marked, generalized pruritus. Results of liver function tests were as follows: serum bilirubin, 8 mg. per 100 cc.; alkaline phosphatase, 20 units per 100 cc.; cephalin flocculation, 2+ after 24 hours; thymol turbidity, 5 units per 100 cc. The urine was dark and positive for urobilinogen and bilirubin. The stools were clay-colored.

After two weeks the stools lost their clay-colored appearance but remained lighter than normal. At this time the serum bilirubin was still 8 mg. per 100 cc. The serum alkaline phosphatase had increased to 26 units; the thymol turbidity was 7 units, and the cephalin flocculation was 2+ after 48 hours.

The patient continued to be markedly jaundiced, and the generalized pruritus persisted for six months. At this time the serum bilirubin was 7 mg. per 100 cc.; thymol turbidity was 7 units; cephalin flocculation was 1+; serum alkaline phosphatase had decreased to 12 units. At this point the jaundice suddenly cleared; two weeks later the patient delivered a normal infant. Since parturition there has been no recurrence of jaundice, and the results of liver function tests have all been within normal limits.

CASE 2.—A 40-year-old woman was seen because of anxiety, hypochondriasis, and intermittent depression. She was started on chlorpromazine, receiving 50 mg. four times daily for two weeks. Suddenly she developed jaundice, associated with extreme itching of the skin, epigastric tenderness, acholic stools, dark urine, nausea, and vomiting. The patient was moderately jaundiced, and the liver was slightly tender and palpable 2 cm. below the costal margin. The results of laboratory studies on admission were as follows: alkaline phosphatase, 17.6 units; cephalin flocculation at 48 hours, 1+; thymol turbidity, 1.8 units; prothrombin, 100%; serum bilirubin, 5.4 mg. per 100 cc.; urinary urobilinogen, trace, and marked bilirubinuria. A complete blood cell count was within normal limits.

The patient was placed on bed rest, with considerable symptomatic improvement. Two weeks later the laboratory studies were repeated, with the following results: alkaline phosphatase, 11 units; serum bilirubin, 2.9 mg.; thymol turbidity, 1.8 units, and urine bilirubin, trace. The blood cell count continued normal.

A liver biopsy showed bile stasis, with cholangiolitic obstruction and hepatic infiltration of lymphocytes, without evidence of hepatocellular destruction. Recovery was uneventful, and liver function studies after one month were all within normal limits.

Comment

The exact pathogenesis of jaundice associated with the administration of chlorpromazine is not clear. The fact that jaundice usually does not appear when the drug is given a second time seems to indicate that jaundice is not an allergic response in the usual sense of the word. Indeed, some investigators report that jaundice clears despite continuance of chlorpromazine therapy. It does seem probable, however, that this type of jaundice is an idiosyncratic response of the patient, and not a pharmacologic effect of the drug.

TABLE 3.—*Compounds Associated with Obstructive Jaundice*

Drug	Cases	Authors
Arsphenamine	12	Hanger and Gutman[8]
Methyltestosterone	7	Werner et al.[9]
Chlortetracycline (Aureomycin)	7	Lepper et al.[10]
Sulfonamides	38	Menten and Anderach[11]
Thiouracil	2	Gargill and Lesses[12]
Propylthiouracil	1	Livingston and Livingston[13]
Diphenylhydantoin (Dilantin)	1	Chaiken[14]
Phenacemide (Phenurone)	31	Tyler and King[15]
Trimethadione (Tridione)	1	Leard et al.[16]
Aminosalicylic acid U.S.P.	1	Cuthbert[17]
Diaminodiphenylsulfone	3	Jelliffe[18]
Isoniazid	3	Committee report, American Trudeau Society[18]
Antergan*	1	LaDues[20]
Dinitrophenol	1	Hanger and Gutman[8]
Methimazole	1	Schipp[21]

* Trade name for dimethylamino-ethyl-benzylamine.

Since the majority of chemicals, endogenous and exogenous, are inactivated or detoxified in the liver, it is not surprising to find this organ involved in toxic reactions resulting from prolonged drug therapy. As a result of the introduction of many new drugs, the number of agents capable of causing toxic hepatitis in man has steadily increased.‡ Table 3 contains a list of compounds that have been implicated in the occurrence of obstructive jaundice similar to that caused by or related to the administration of chlorpromazine.

Although the time of onset of icterus varies from drug to drug, a striking similarity in histological and biochemical findings exists between cases of jaundice resulting from therapy with thiouracil, methimazole U. S. P., methyltestosterone, arsphenamine, and chlorpromazine. In all of these cases histological examinations reveal the presence of a dark-staining material in the canaliculi around the central vein, which is thought to be "bile thrombi." Occasionally, cellular infiltration was observed in the periportal area. Damage to liver cells was never observed. Results of liver function studies were usually normal with the exception of serum alkaline phosphatase, serum cholesterol, and serum bilirubin, which were elevated. Urinalyses generally showed the presence of bile; stools were usually acholic. Except for an occasional increase in the eosinophil count, blood counts were normal. Physical findings were much the same and included general malaise, pruritus, anorexia, chills, and/or fever.

Since none of these drugs produce a direct effect on hepatic cells, the mechanism underlying jaundice is unclear, but may be related to some physiological disturbance rather than an organic pathology. It is known that factors that influence normal physiological patterns often render a person more vulnerable to the action of a substance which is otherwise relatively nontoxic. Pregnancy, vomiting, anorexia, and preceding debilitating illness may lead to a conditioned protein deficiency, which, added to the impact of a drug, may lead to hepatic insufficiency and jaundice.§ A history of chronic alcoholism or venereal disease also predisposes a patient to severer hepatitis from drugs.‖ In the case of chlorpromazine, it is barely possible that the drug might act to augment autonomic imbalance and produce bile stasis through some nervous system mechanism. It has been reported [25] that in animals chlorpromazine increases the tone of the biliary sphincter, thus raising biliary intraductal pressure. This may be one factor in the production of jaundice.

The lack of jaundice associated with the administration of other chlorinated phenothiazines (thiodiphenylamines) tends to disprove the belief that the halogen moiety is responsible for hepatotoxic reactions.[26]

There has been some speculation [27] about the relationship between hepatic and extrapyramidal complications produced by chlor-

‡ References 8-24.

§ References 17, 18.

‖ References 17, 19.

promazine. An involvement of these two systems is, of course, found in Wilson's disease (hepatolenticular degeneration). However, we are of the belief that the similarity is coincidental. Both CNS and hepatic changes are quite distinct in the two conditions.

The clinician cannot ignore the potential hepatotoxicity of chlorpromazine. In our experience this complication has, however, been overemphasized. It is relatively infrequent and with proper management should not cause trouble. There are few drugs which have more varied side-effects than chlorpromazine, but, in spite of this, fatal outcome is very rare indeed. In the presence of clear indications for the use of chlorpromazine, we do not hesitate to take the very slight risk of producing a reversible jaundice.

Summary

The hepatic function of 30 medical and 33 psychiatric patients under treatment with chlorpromazine was studied.

No changes were found, and it is considered that routine liver function tests are of no value for predicting the development of hepatotoxicity.

The etiology of jaundice following chlorpromazine and other drugs is discussed, and two case histories are presented.

REFERENCES

1. Doughty, R. B.: The Incidence of Jaundice Associated with Chlorpromazine Therapy, in Symposium: Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955, pp. 196-197.

2. Lemire, R. E., and Mitchell, R. A.: Regurgitation Type Jaundice Associated with Chlorpromazine (Thorazine, SKF 2601-A) Administration, J. Lab. & Clin. Med. 44:825, 1954.

3. Van Ommen, R. A., and Brown, C. H.: Obstructive-Type Jaundice Due to Chlorpromazine (Thorazine): Report of 3 Cases, J. A. M. A. 157: 321, 1955.

4. Zatuchni, J., and Miller, G.: Jaundice During Chlorpromazine Therapy, New England J. Med. 251:1003, 1954.

5. Cohen, I. M., and Archer, J. D.: Liver Function and Hepatic Complications in Patients Receiving Chlorpromazine, J. A. M. A. 159:99, 1955.

6. Kelsey, J. R., Jr.; Moyer, J. H.; Brown, W. G., and Bennett, H. D.: Chlorpromazine Jaundice, Gastroenterology 29:865, 1955.

7. Moyer, J. H.; Kinross-Wright, V., and Finney, R. M.: Chlorpromazine as a Therapeutic Agent in Clinical Medicine, A. M. A. Arch. Int. Med. 95:202, 1955.

8. Hanger, F. M., and Gutman, A. B.: Postarsphenamine Jaundice, J. A. M. A. 115:263, 1940.

9. Werner, S. C.; Hanger, F. M., and Kritzler, R. A.: Jaundice During Methyl Testosterone Therapy, Am. J. Med. 8:325, 1950.

10. Lepper, M. N.; Wolfe, C. K.; Zimmerman, H. J.; Caldwell, E. R., Jr.; Spies, H. W., and Dowling, H. F.: Effect of Large Doses of Aureomycin on Human Liver, A. M. A. Arch. Int. Med. 88:271, 1951.

11. Menten, H., and Andersch, L. J.: Hepatic Damage Associated with Sulfonamide Therapy in Infants and Children, Ann. Int. Med. 19:609, 1943.

12. Gargill, S. L., and Lesses, M. F.: Toxic Reactions to Thiouracil, J. A. M. A. 127:890, 1945.

13. Livingston, H. J., and Livingston, S. F.: Agranulocytosis and Hepatocellular Jaundice, J. A. M. A. 135:422, 1947.

14. Chaiken, B. H.; Goldberg, B. I., and Segal, J. P.: Dilantin Sensitivity, New England J. Med. 242:897, 1950.

15. Tyler, M. W., and King, E. Q.: Phenacemide in Treatment of Epilepsy, J. A. M. A. 147: 17, 1951.

16. Leard, S. E.; Greer, W. E. R., and Kaufman, T. C.: Hepatitis, Exfoliative Dermatitis and Abnormal Bone Marrow Occurring During Tridione Therapy, New England J. Med. 240:962, 1949.

17. Cuthbert, J.: Acquired Idiosyncrasy to Sodium *p*-Aminosalicylate, Lancet 2:209, 1950.

18. Jelliffe, D. B.: Toxic Hepatitis Caused by Diaminodiphenylsulphone, Lancet 1:1343, 1951.

19. Ebert, R. H., and others: The Toxicity of Isoniazid: A Report of the Committee on Therapy, American Trudeau Society, Am. Rev. Tuberc. 68: 302, 1953.

20. LaDuea, N.: Epatonefrite mortale da Antergan, Diagnose 3:137, 1947.

21. Shipp, J. C.: Jaundice During Methimazole ("Tapazole") Administration, Ann. Int. Med. 42: 701, 1955.

22. Himsworth, H. P., and Glynn, L. E.: Toxipathic and Trophopathic Hepatitis, Lancet 1:457, 1944.

23. Abell, M. R., and Beveridge, J. M. R.: Studies on Hepatic Necrosis Induced by Dietary Means: IV. Conditions Affecting the Production and Prevention of Massive Liver Necrosis, A. M. A. Arch. Path. 52:428, 1951.

24. Hardy, H. L., and Feemster, R.: Infectious Hepatitis in Massachusetts, New England J. Med. 235:147, 1946.

25. Menguy, R. B.; Bollman, J. L.; Grindlay, J. H., and Cain, J. B.: Biliary Stasis Produced by Chlorpromazine: An Experimental Study, Proc. Staff Meet. Mayo Clin. 30:601, 1955.

26. Kinross-Wright, V.: Clinical Trial of a New Phenothiazine Compound—NP-207, Psychiat. Res. Rep. 4:89, 1956.

27. Azima, H., and Richman, A.: Alteration of Copper Metabolism in Chlorpromazine-Treated Cases, A. M. A. Arch. Neurol. & Psychiat. 75: 163, 1956.

Books

Les Thérapeutiques psychiatriques. By Henri Baruk. Pp. 127. Presses universitaires de France, 108 boulevard Saint-Germain, Paris, 1955.

This is one of a popular series of small pamphlets which purport to give brief statements of the present state of our knowledge concerning various matters of interest to the general public. Baruk has written two others of this series, one on "Psychoses and Neuroses" and another on "Social Psychiatry."

The present volume proposes to give a brief account of the methods used for the treatment of mental disorders, in a first part, and of the art of applying these treatments, in a second part. The second part is, however, only five pages long and consists essentially of the statement that the essential of the cure is the art of the physician. Baruk deplores the tendency at the present time to be satisfied with an incomplete and general diagnosis and a rule-of-thumb treatment. He remarks on the fact that young psychiatrists lack the knowledge and experience of the great clinicians of the past, such as Séglas or de Clérambault, which enabled them to adapt their treatment to the infinite variability of the clinical manifestations.

The first (and major) part of the book passes in review the various forms of treatment, dividing them as follows:

1. Those which aim to calm the patient's irritability either temporarily or definitively; they range through electroshock, various comas, and psychosurgery
2. Those which aim to treat the somatic causes of the disease, whether these causes be cerebral or extracerebral.
3. Those which aim to control the symptoms by drugs or hygienic methods, such as rest, hydrotherapy, etc.
4. Those which are aimed directly at the patient's mind (psychotherapy)
5. Methods of reeducation and resocialization

The author does not confine himself to a description of these therapeutic techniques, but enters into a critique of their uses and abuses, which it would be impossible to reproduce here in detail. Many of his criticisms are general knowledge in the profession. He is most critical of such procedures as lobotomy that create permanent defects in the brain, which, after all, is the most important organ of our behavior. He quotes with approval Maimonides, who wrote: "I call him a perfect physician who sometimes judges it better to abstain from treatment rather than prescribe one which might perturb the course of the malady." In speaking of those practitioners who give electroshock to their patients without, or with only a cursory, examination, he quotes again Maimonides: "Only charlatans believe themselves to be infallible; for them difficult and complicated cases do not exist. They maintain even that reflection over a case is a waste of time."

As might be expected, because of his own extensive studies of the etiological biological factors in the causation of mental derangements, the author discusses at length the bacteriological, toxic, endocrine, degenerative, and other organic factors and the physiological treatments based upon them. For the social factors the reader is referred to the author's discussion in another pamphlet of the same collection. He insists on the importance of treating the entire family of the patient and gives interesting examples of this necessity.

There is an interesting section on which the author calls his chitamnic method. The word chitamnia is derived from two Hebrew words (*chitah*, method, and *aemounah*, confidence). It refers to the attitude of the physician and implies that he should work simultaneously with his heart and his intelligence in order that his intelligence may not stifle his heart and also that his heart may not stifle his lucidity and the meticulous and impartial search for the truth. This is a principle of justice which in the Bible is called *tsedek*. This method is at once individual and social, since it supposes a considerable effort on the part of the physician to take into consideration himself (and his attitudes), the patient, and the milieu, with a profound respect for the search after the truth. This method is discussed in detail in the author's book "Psychiatrie morale."

The author criticizes methods of psychotherapy based on dogmatic systems of theory and pleads for flexibility in the face of the complexities of the clinic. He thinks the great danger

in psychotherapy is to impose in advance on all the patients the distortion of an accepted viewpoint as seen through a dogmatic lens, which results in enclosing patient and physician in a closed system. He quotes with admiration "the great clinician Babinski, who, when he examined a patient, concentrated his whole personality toward an examination so meticulous, so scrupulous, and so exact that he was accustomed to say: 'Let me permit myself to be penetrated by the patient,' an admirable maxim and example of professional conscience, science and modesty." The author speaks with approval of the psychosomatic movement, while noting that is nothing new, and insists on the need of the psychiatrist to have a general medical culture. He is opposed to narcoanalysis on the ground that it violates the personality of the patient, which the orthodox psychoanalytic procedure of Freud never did.

This is an admirable little manual which gives concisely the attitude toward the popular methods of therapy of one of the most articulate and appreciated of the French psychiatrists.

The Menninger Story. By Walker Winslow. Price $5.00. Pp. 350. Doubleday & Company, Inc., Garden City, N. Y.; 575 Madison Ave., New York 22, 1956.

A phenomenon which has been important to American Medicine, namely, the establishment by individuals or families of great clinics and training centers without initial association with universities, is documented in this volume in relation to the Menninger Clinic, as has previously been done in the case of the Mayo Clinic (Clapesattle, H. B.: The Doctors Mayo, Minneapolis, University of Minnesota Press, 1941).

The problem undertaken by Walker Winslow in this book is impressive in its scope, for adequate understanding of the founding and growth of the Topeka clinic involves understanding of the lives of three men, both individually and as they are mutually affected by their interrelationships.

The author has not flinched in the face of this challenge, and, except for a certain enthusiasm which has prevented him from placing the Menninger Clinic in proper perspective in relation to other important modern influences in American psychiatric training and practice, he has succeeded in indicating the major forces which have molded the clinic into its present form and in underlining the more important areas of its influence and of the influence of the Menningers individually. Thus, Dr. William Menninger's work in helping to revise military psychiatric concepts during World War II is emphasized; the importance of Dr. Karl Menninger's effect on psychiatric practice in the Veterans Administration is pointed up, and the organization and administration of a large training program for psychiatric residents at the Clinic and at Winter VA Hospital are adequately described.

This volume will be of interest to those who would like to know of the genesis of the Menninger Clinic, both for its own sake and as an example of the small private clinic grown to important teaching, training, and research stature, such as has appeared from time to time in American Medicine, and which demands understanding and appreciation as an important segment of our medical structure.

for those with

PARKINSONISM

Smoother activity

and

brighter expression

with '**KEMADRIN**'®*

- reduces rigidity and tremor.
- seldom causes dryness of the mouth, blurring of vision or excitation.

*'**KEMADRIN**' brand Procyclidine Hydrochloride Tablet of 5 mg., scored. Bottles of 100 and 1,000.

Literature available on request.

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, N.Y.

All of these articles have appeared in TODAY'S HEALTH and are now available in one pamphlet.

ALCOHOLISM

an important problem in today's living

ALCOHOLICS ANONYMOUS

Written from the standpoint of a member, the basic treatment procedures are described and the psychological problems confronting the alcoholic are discussed.

ALCOHOL AND CIRRHOSIS OF THE LIVER

Relationship between alcohol, diet and cirrhosis. Increasing stress on nutritional differences.
by Russell S. Boles

HOW TO HELP A PROBLEM DRINKER

Understanding the alcoholic's capabilities, the necessity of help, causes of his condition.
by Edward A. Strecker and Francis T. Chambers, Jr.

THE TREATMENT OF ALCOHOLISM

Tracing the steps from convincing the alcoholic that he is sick through treatment and cure.
by Lewis Inman Sharp

CONDITIONED REFLEX TREATMENT OF CHRONIC ALCOHOLISM

Its place among methods of treatment today, its development and correlation with personality factors.
by Walter L. Voegtlin

INSTITUTIONAL FACILITIES FOR THE TREATMENT OF ALCOHOLISM

Comparative differences, in drinking, with the last century, new establishments and methods of treatment, lack of trained personnel.
by E. H. L. Corwin

THE ABOVE SIX PAMPHLETS ARE AVAILABLE IN BOOKLET FORM FOR ONLY 50 CENTS

HOW EXPERTS MEASURE DRUNKENNESS

A partial transcript of an actual courtroom case.
H. A. Heise
8 pages, 15 cents

BARBITURATES, BOOZE AND OBITUARIES

A discussion of the dangers of mixing alcohol and barbiturates.
Donald A. Dukelow
4 pages, 10 cents

ADDRESS REQUESTS TO:

ORDER DEPARTMENT
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

when your patients need to be

stimulated

not tranquilized

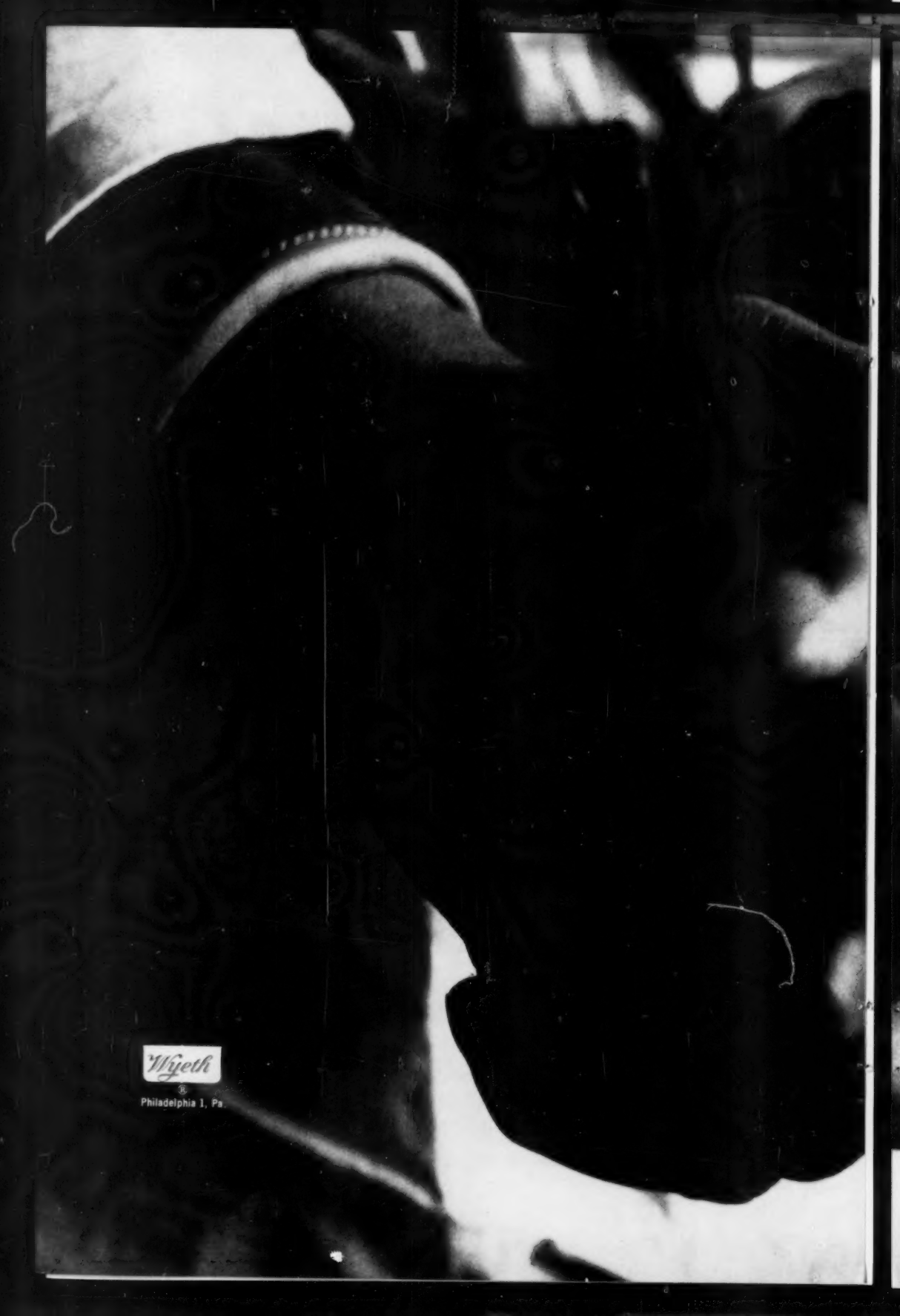
You will find that 'Dexedrine'—a standard antidepressant—helps dispel apathy and lethargy, restoring optimism, energy and a sense of well-being in your depressed patients. 'Dexedrine' is available as tablets, elixir, and Spansule† sustained release capsules.

Smith, Kline & French Laboratories, Philadelphia

Dexedrine*

*T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

†T.M. Reg. U.S. Pat. Off.


Wyeth
Philadelphia 1, Pa.

TO REMOVE RESTRAINTS
The dramatic control of acute psychotic agitation achieved with SPARINE "... permits patients who would ordinarily require restraints to participate in ward activities and care for themselves."1
Toxicity with SPARINE is minimal—no case of liver damage has been reported.
SPARINE is also highly effective in drug addiction and alcoholism for the control of withdrawal symptoms.
1. Fazekas, J.F., et al.: J.A.M.A. 161:46 (May 5) 1956
Professional literature available upon request.
Sparine*
HYDROCHLORIDE
Promazine Hydrochloride
10-(γ-dimethylamino-n-propyl)-phenothiazine hydrochloride
*Trademark

INDEX TO
NEUROPSYCHIATRIC INSTITUTIONS SPECIAL SCHOOLS and SANITARIA Advertising in A.M.A. Archives of NEUROLOGY and PSYCHIATRY

Display announcements of the following institutions appear regularly in A. M. A. Archives of NEUROLOGY and PSYCHIATRY. For advertisements of those institutions which run on an every-other month basis it would be necessary to consult the advertising section of a previous or *subsequent issue*.

ADAMS HOUSE ..... **Boston, Jamaica Plain, Mass.**
James Martin Woodall, M.D., Medical Director

APPALACHIAN HALL ..... **Asheville, N. C.**
Wm. Ray Griffin, M.D.

BALDPATE ..... **Georgetown, Mass.**
G. M. Schlomer, M.D.

BEVERLY FARM, INC. ..... **Godfrey, Ill.**
Dr. Groves B. Smith, Superintendent

FAIRVIEW SANITARIUM ..... **Chicago, Ill.**
Dr. J. Dennis Freund, Medical Director

HALL-BROOKE ..... **Greens Farms, Conn.**
Dr. Geo. S. Hughes, Medical Director

LIVERMORE SANITARIUM ..... **Livermore, Calif.**
O. B. Jensen, M.D., Superintendent and Medical Director

MENNINGER FOUNDATION ..... **Topeka, Kan.**
J. Cotter Hirschberg, M.D., Director

MILWAUKEE SANITARIUM FOUNDATION, INC. ..... **Wauwatosa, Wis.**

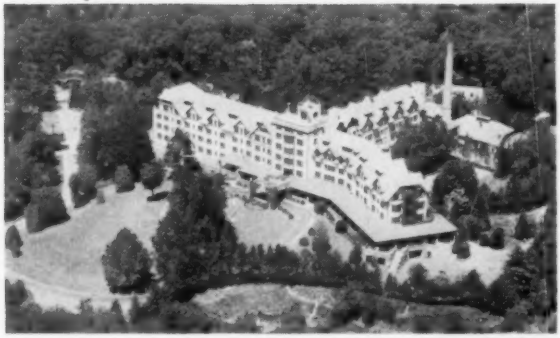
NORTH SHORE HEALTH RESORT ..... **Winnetka, Ill.**
Samuel Lichman, M.D., Medical Director

THE RING SANATORIUM ..... **Arlington, Mass.**
Benjamin Simon, M.D., Director

RIVER CREST SANITARIUM ..... **Astoria, Queensboro, N. Y. City**
and **BELLE MEAD FARM COLONY** ..... **Belle Mead, N. J.**
Dr. J. J. Kindred, Founder and Consultant

Appalachian Hall

Established 1916
Asheville, North Carolina



An Institution for the diagnosis and treatment of Psychiatric and Neurological illnesses, rest, convalescence, drug and alcohol habituation.
Insulin Coma, Electroshock and Psychotherapy are employed. The Institution is equipped with complete laboratory facilities including electroencephalography and X-ray.
Appalachian Hall is located in Asheville, North Carolina, a resort town, which justly claims an all around climate for health and comfort. There are ample facilities for classification of patients.

WM. RAY GRIFFIN, JR., M.D. — MARK A. GRIFFIN, SR., M.D.
ROBERT A. GRIFFIN, M.D. — MARK A. GRIFFIN, JR., M.D.

For further information write APPALACHIAN HALL, ASHEVILLE, N. C.

North Shore Health Resort

on the shores of Lake Michigan
WINNETKA, ILLINOIS

NERVOUS and MENTAL DISORDERS
ALCOHOLISM and DRUG ADDICTION

Modern Methods of Treatment

MODERATE RATES

Established 1901 — ***Accredited by The Joint Commission on Accreditation of Hospitals***
Licensed by State of Illinois

SAMUEL LIEBMAN, M.S., M.D.
Medical Director

225 Sheridan Road — **Winnetka 6-0211**

HALL-BROOKE

An Active Treatment Hospital

A licensed private hospital devoted to active treatment, analytically-oriented psychotherapy, and the various somatic therapies.

A high ratio of staff to patients.

Large occupational therapy building with a trained staff offers complete facilities for crafts, arts and recreation. Full program of outdoor activities.

Each patient is under constant, daily psychiatric and medical supervision.

Located one hour from New York on 120 acres of Connecticut countryside.

HALL-BROOKE

Greens Farms, Box 31, Conn., Tel.: Westport, CApital 7-5105

George S. Hughes, M.D.
Leo H. Berman, M.D.
Alfred Berl, M.D.
Louis J. Micheels, M.D.

Robert Isenman, M.D.
John D. Marshall, Jr., M.D.
Peter B. Barbara, Ph.D.
Mrs. Heide F. Bernard and
Samuel Bernard, Administrators

NEW YORK OFFICE, 46 East 73 Street
Telephone: Lehigh 5-5155

RIVER CREST SANITARIUM

FOR

NERVOUS, MENTAL, AND ALCOHOLIC PATIENTS

Layman R. Harrison, M.D.
Physician in Charge

Martin Dollin, M.D.
Clinical Director

Russell N. Carrier, M.D.
Consultant in Psychotherapy

Arthur Gordon, M.D.
Consultant in Medicine

Katherine C. Kindred
Administrator

Approved for resident training in Psychiatry

A private hospital for the care and treatment of nervous and mental disorders. All accepted types of treatment available. Individualized attention to psychotherapy, insulin and electroshock therapy.

A cottage maintained expressly for elderly women with problems of senility and continued care. We also have accommodations for men requiring continued care.

River Crest is located in a beautifully wooded and landscaped park of about twelve acres, secluded but easily accessible by subway, bus or private car.

Full cooperation with referring physicians, who will find it convenient to visit or participate in the treatment of their patients while at River Crest.

Ditmars Boulevard and 26th Street
ASTORIA, L. I., NEW YORK CITY
AS 8-0820

TWENTY MINUTES FROM TIMES SQUARE

ADAMS HOUSE

Established 1877

☆

A non-commitment sanitarium and clinic, club-like in physical setting and atmosphere, applying re-educational psychotherapeutic methods in the study and treatment of the **psychoneuroses** exclusively.

Located in suburban Boston contiguous to and overlooking the Arnold Arboretum

☆

James Martin Woodall, M.D., Medical Director

990 CENTRE STREET, BOSTON,
Jamaica Plain, MASS.

BALDPATE, Inc.

Georgetown, Mass.

Geo. Fleetwood 2-2131

Located in the hills of Essex County, 30 miles north of Boston

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Occupation under a trained therapist, diversions and outdoor activities.

HARRY C. SOLOMON, M.D. — *Consulting Psychiatrist*
GEORGE M. SCHLOMER, M.D. — *Medical Director*

"Doctor, will you tell me..."

What are the symptoms?
How shall I treat it?
What causes it?

For practical information about communicable disease, have your patients read:

SCARLET FEVER
8 pages, 15 cents

IMMUNIZATION
by Ruth A. Thomas, 8 pages, 15 cents

WHOOPING COUGH
by Constance Frick, 4 pages, 10 cents

PNEUMONIA'S WATERLOO?
by William W. Bolton, 12 pages, 15 cents

WE CAN PREVENT DIPHTHERIA
by P. S. Rhoads, 8 pages, 15 cents

AMERICAN MEDICAL ASSOCIATION • 535 NORTH DEARBORN • CHICAGO 10

FAIRVIEW Sanitarium

2828 S. PRAIRIE AVE.
CHICAGO
Phone VIctory 2-1650
J. DENNIS FREUND, M.D.
Medical Director

DEVOTED TO THE ACTIVE TREATMENT OF

MENTAL and NERVOUS DISORDERS

Specializing in Psycho-Therapy, and Physiological therapies including:

- Insulin Shock
- Electro-Shock
- Electro-Narcosis
- Out Patient Shock Therapy Available

ALCOHOLISM Treated by Comprehensive Medical-Psychiatric Methods.

RING SANATORIUM

Eight Miles from Boston—Founded 1879

For the study, care, and treatment of emotional, mental, personality, and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.

Full resident and associate staff. Courtesy privileges to qualified physicians.

BENJAMIN SIMON, M.D.
Director

CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights, Massachusetts

MIssion 8-0081

THE SOUTHARD SCHOOL

Intensive individual psychotherapy in a residential school, for children of elementary school age with emotional and behavior problems.

THE MENNINGER CHILDREN'S CLINIC

Outpatient psychiatric and neurologic evaluation and consultation for infants and children to eighteen years.

Department of Child Psychiatry

THE MENNINGER FOUNDATION

J. Cotter Hirschberg, M.D., Director — **Topeka, Kansas; Telephone 3-6494**

"Beverly Farm"

INCORPORATED
Founded 1897
INCORPORATED 1922

12 buildings
220 acres of land
300 feet above
Mississippi River

HOME AND SCHOOL FOR
Nervous and Backward Children

Can accommodate 350 children, with contemplated educational improvements for a larger number. Can accept some suitable case for life.

Address all communications to DR. GROVES B. SMITH, SUPERINTENDENT
"Beverly Farm" GODFREY, MADISON COUNTY, ILLINOIS

THE LIVERMORE SANITARIUM and PSYCHIATRIC CLINIC

Livermore, California

Telephone: Hilltop 7-3131

Oakland Office—411 30th Street

FOR THE TREATMENT OF NERVOUS AND MENTAL DISORDERS

THE OPEN CONVALESCENT DEPARTMENT, for nervous and general patients; the COTTAGE DEPARTMENT, for mental patients. Features: near Oakland and San Francisco; ideal climate; large beautiful grounds; hydrotherapy, athletic and occupational departments; clinical laboratory; large nursing force. Rates include room, suitable diet, medical care, general nursing and routine examinations.

HERBERT E. HARMS, M.D.—Superintendent

THE DEVEREUX FOUNDATION

Since 1940, non-profit sponsor of

DEVEREUX SCHOOLS

Established 1912

THERAPEUTIC SCHOOLS
VOCATIONAL COMMUNITIES
REMEDIAL CAMPS

SCHOOLS

EARL D. BOND DIVISION — Pennsylvania
WALTER L. TREADWAY DIVISION — California

A complete scholastic program, in residence, for boys and girls presenting emotional difficulties, who can benefit by a program of therapeutic education, supplemented by psychoanalytic therapy, where indicated.

Separate facilities and campuses for different age groups, from pre-kindergarten through junior college.

COMMUNITIES

LEO KANNER DIVISION — Pennsylvania
RANCH DIVISION — California

"Life-experience" and vocational programs for children, adolescents, and young adults with impaired intellectual or CNS function.

Separate, self-contained campuses for homogeneous groups, in terms of age and social maturity.

CAMPS

PENNSYLVANIA — MAINE — CALIFORNIA

Each Devereux School or Community has its own individual camp. Remedial academic programs, full recreational facilities, permit therapy to continue through the long summer holiday.

Professional inquiries will be welcomed by JOHN M. BARCLAY, *Director of Development*
Devereux Foundation, Devon, Pennsylvania

Devereux Schools

UNDER THE DEVEREUX FOUNDATION

HELENA T. DEVEREUX, *Director*

Professional Associate Directors

ROBERT L. BRIGDEN, Ph.D. — EDWARD L. FRENCH, Ph.D.
MICHAEL B. DUNN, Ph.D. — ROBERT T. GRATTAN, M.D.
J. CLIFFORD SCOTT, M.D.

Santa Barbara, California — **Devon, Pennsylvania**

Comment on the use of 'Thorazine' in a mental hospital:

"we have ceased to regard any of our patients as 'incurable'"

"Admittedly our recovery rates have tended to decrease progressively as chronicity increases. However, we have encountered several seemingly 'miraculous' responses in patients hospitalized ten years or more and previously regarded as just about hopeless."[1]

THORAZINE* is available in ampuls, tablets and syrup (as the hydrochloride), and in suppositories (as the base).

'Thorazine' should be administered discriminately and, before prescribing, the physician should be fully conversant with the available literature.

For information write: *Smith, Kline & French Laboratories, Philadelphia 1*

1. Yohe, C.D.: in Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.